American Heart Journal

An international publication for the study of the circulation

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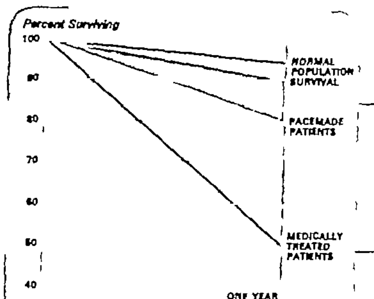
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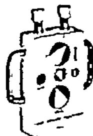




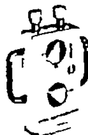
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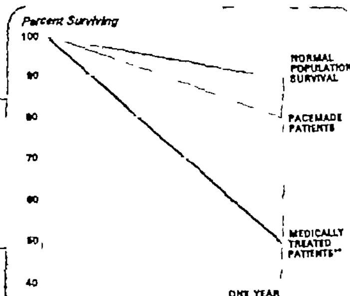
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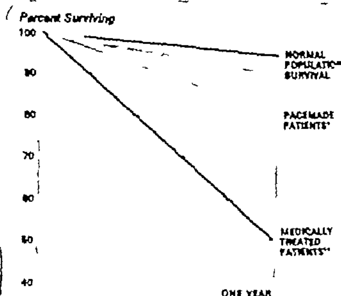
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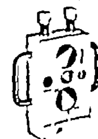
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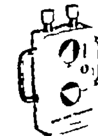
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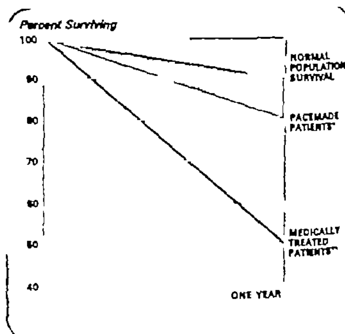
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Editorial

The prevention of late deaths after myocardial infarction

R. R. H. Lovell, M.D.(Lond.), F.R.C.P., F.R.A.C.P.
Melbourne, Australia

Until well into the 1950's what is generally diagnosed today as myocardial infarction was often called coronary thrombosis though the use of the alternative term coronary occlusion implied that blocks in coronary arteries might not always be thrombotic. At that time reports of the frequency with which myocardial infarction was associated with thrombosis varied greatly but the prevailing belief was that, while there were other causes, coronary thrombosis was the commonest precipitating factor. This belief and the notion that survivors of an infarct most often died of another one, naturally led to consideration of long-term anticoagulant administration as a possible way of improving long-term survival. The evaluation of this prophylactic or secondary preventive treatment has proved difficult, largely for numerical reasons and because of variations in the formats in which results have been published. After 24 years the balance of evidence reviewed up to 1964 and supplemented by more recently reported large studies[2] is that anticoagulants improve survival after recovery from the acute stage of myocardial infarction. The mortality rate for younger men who leave the hospital and continue anticoagulant therapy may be reduced by 30 per cent over a two year period. Clearly, however, there is a limit to their effectiveness. This limit could exist because anticoagulants are not very efficient at preventing recurrent coronary thrombosis. On the other hand their effect on the mortality rate might also be limited if mechanisms other than thrombosis precipitate a substantial proportion of deaths in these patients.

Further light may be thrown on these questions by considering the causes of deaths in patients in controlled trials of long-term anticoagulant administration. The difficulty in an analysis of this sort is the absence of comprehensive or fully representative postmortem observations. In all the trials postmortem observations have been far from complete and factors determining whether postmortem examinations have been done or not have varied according to modes and circumstances of death. To try to overcome this difficulty a group from Melbourne, Australia, has approached the matter by stating criteria by which the modes of death of all their patients could be classified. The 76 deaths occurring in this trial were distinguished as occurring (1)

From the University of Melbourne Department of Medicine, The Royal Melbourne Hospital, 3050 Victoria, Australia.

suddenly (2) after chest pain and (3) in other ways. The findings were that most deaths were in the first two classes and that while deaths after chest pain were fewer than expected in patients dying while taking anticoagulant tablets the proportion of sudden deaths was the same as in patients taking control tablets.

Few of the reports of other trials provide full information on modes of death and when deaths have been classified by cause the criteria for the classification have not always been explicitly stated. Table I summarizes the reported data on patients who died suddenly and those who died from reinfarction. In general they reveal a pattern similar to that described in the Melbourne study.

In this connection Leren's[11] observations on survivors from myocardial infarction treated with a cholesterol lowering diet are interesting. The patients had initially remarkably high cholesterol levels (average about 295 mg. per 100 ml.). He found that the dieted group suffered fewer myocardial infarctions than the control subjects, but their risk of sudden death remained the same (see table). Perhaps, in hypercholesterolemic men a low cholesterol diet acts in the same way as anticoagulants, albeit more slowly.

These observations provoke a number of thoughts. First, the idea that the commonest cause of death after recovery from myocardial infarction is another myocardial infarction is questionable and anyway an oversimplification. Many, perhaps half, of these patients die suddenly. Unlike patients dying soon after developing symptoms of myocardial infarction, in those dying suddenly there are frequently no *signs of recent thrombosis or infarction* even with the most thorough postmortem examination.[12,13] Confusion of thinking has arisen from the frequent use of the term myocardial infarction to include sudden deaths.

Second, judged by their ability to reduce deaths due to recurrent myocardial infarction as well as to reduce recurrent nonfatal myocardial infarction, anticoagulants seem quite effective, and the more rigorously prothrombin activity is controlled the more effective they appear to be.[4] Their effect on survival is limited by two factors. One is the difficulty in sustaining their efficient administration, even within the discipline of a controlled trial in a specialist center. The other factor is that their mode of action is evidently irrelevant to the mechanism precipitating many sudden deaths which account for upwards of half the late mortality.

Two approaches to the problem of secondary prevention are indicated by these considerations. One is the attainment of more practicable and efficient anticoagulation. This involves the further identifica

Table I. Deaths after recovery from myocardial infarction

Author	No. of patients		Sudden deaths*		Deaths due to probable recurrent infarction†	
	Comparative	Anticoagulant	Comparative	Anticoagulant	Comparative	Anticoagulant
Bjerkelund	118	119	9	5	21	9
Brown et al.	34	37	1	6	2	3
Aspenstrom and Korsan Bengtsen[14]	91	88	24	22	14	5
V. A.	359	358	39	44	39	28
Lovell et al.	178	172	13	14	17	7
Loelinger et al.	122	128	4	7	5	1
Leren[11]	206	206‡	27	27‡	25	10‡

*Cause of death was sudden death [illegible]; sudden, not defined [illegible]; sudden and unexplained.
†Certain or probable reinfarction; myocardial infarction; chest pain before death; cardiac symptoms before death; several criteria.
‡Leren's patients were treated by diet therapy rather than anticoagulants.

tion of patients who are and who are not likely to derive worthwhile benefit, and the evaluation in properly controlled trials of drugs, such as those affecting platelets, which by mechanisms other than depression of prothrombin activity might diminish the tendency for recurrent thrombosis to occur

The other approach is an evaluation of measures which might diminish the tendency for sudden death to occur The mechanism of sudden death other than when it is precipitated by coronary thrombosis, recurrent infarction or rupture of the ventricle is thought to reflect sudden disturbances in contraction of the heart resulting in ventricular fibrillation or standstill. The Melbourne study suggests that patients at particularly high risk of sudden death may be detectable in advance Twenty per cent of patients with major arrhythmias noted in the hospital (at a time when relatively few patients were being routinely monitored) died suddenly during a follow-up of up to three years compared with only 7 per cent of those who had not had an arrhythmia noted Detailed follow-up of many more patients who have had electrocardiographic monitoring during their acute infarct is needed to discover if the risk may be more clearly related to some sorts of arrhythmias and not to others. At the same time, the stage is set for controlled trials of long term prophylactic administration of such antiarrhythmic drugs as seem safe to test in a postinfarct group Since the increased risk of death in patients who have had an arrhythmia with their acute episode is chiefly in the first 12 months after discharge from hospital and since their mortality in this period is about 30 per cent, neither the duration of such trials nor the number of patients needing to be studied to evaluate therapy is as forbidding as has been the case with long term anticoagulant administration.

It would be idle to suppose that the life expectancy statistic for patients who have recovered from acute myocardial infarction which may already be pushed upward by anticoagulant prophylaxis will be the same as for the general population But a decrease in the number of sudden deaths after leaving the hospital might further increase the life expectancy statistic for these patients. Many of the patients at risk have recovered well from their acute illness and have hearts such as have been described as too good to die. [14]

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Clinical communications

The mechanism of bidirectional tachycardia

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The human intraventricular conduction system has always been considered bifascicular. However, this system also is and operates as trifascicular, its three main terminal fascicles being the right bundle branch and the two divisions, anterior and posterior, of the left bundle branch. Evidence for the *trifascicularity of the conduction system* has appeared extensively in the literature[illegible] and this fact has shed new light on many aspects of everyday electrocardiography. This is especially true for the *left anterior* (*LAH*) and *left posterior* (*LPH*) ***hemiblocks*** (blocks in the anterior and posterior divisions, respectively, of the left bundle branch), either alone or combined with right bundle branch block (RBBB). Furthermore, the trifascicularity of the conduction system has also led to the discovery of: (1) the existence of a new family of electrocardiographic syndromes, the intraventricular trifascicular blocks;[illegible] (2) the existence of a new type of "divisional" left bundle branch block (LBBB);[illegible] (3) the different manifestations of aberrant ventricular conduction of supraventricular premature beats.[illegible] (4) In addition, it has rendered possible a new approach to the old problem of the determination of the place of origin of ventricular extrasystoles, and in this field it permitted to predict and then substantiate that left ventricular extrasystoles must necessarily furnish two main, very definite and diametrically opponent ÂQRS directions.[illegible] In this paper we shall try to show how the trifascicularity of the intraventricular conduction system also enables us to explain a curious cardiac arrhythmia, the so-called bidirectional tachycardia (BT), which has so far resisted every attempt at accurate interpretation. As we shall see, BT is nothing but a syndrome of paroxysmal trifascicular block occurring during some episodes of supraventricular tachycardia.

Electrocardiographic features

A typical case of bidirectional tachycardia. Fig. 1 shows a typical ECG of BT. Leads I to III, as well as aV_R, aV_L, and aV_F, were simultaneously recorded with V_1. V_2 to V_6 were recorded simultaneously with the three standard leads (in a four channel machine) to ascertain the correspondence of the two types of QRS complexes in the different leads.

In the standard leads, the first beat shows

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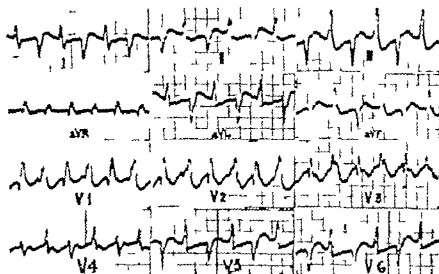


Fig. 1 A typical example of bidirectional tachycardia. Regular rhythm of 142 beats per minute and alternation of two types of ventricular complexes One type (the first beat in every lead) with an ÂQRS at −80 degrees and a pattern of RBBB with LAH the second type, with an ÂQRS at +120 degrees and pattern of RBBB with LPH.

an ÂQRS at −80 degrees with qRs in Lead I and rS in Leads II and III in contradistinction the second beat exhibits an ÂQRS at +120 degrees with rS in Lead I and qR in Leads II and III Namely the first beat has the configuration and ÂQRS direction of LAH and the second beat the configuration and ÂQRS direction of LPH both associated with an RBBB pattern The third and fourth beat as well as the beats which follow exactly reproduce this alternant sequence In the other leads, the first beat is always of the RBBB with the LAH type the second is of the RBBB with the LPH type and so on

In the chest leads there is RBBB pattern in every beat In V although no alternation in polarity occurs there is, in turn alternation in the QRS morphology i.e. qR (or rsR) complexes, corresponding to the beats with LAH alternate with complexes of the R type which correspond to the beats with LPH A similar morphologic alternation occurs in V and V V is transitional and V and V exhibit clear alternant opponency

The interval from the first to the second QRS complex measures 0.4 sec in Lead II and the same time interval of 0.4 sec separates the second from the third T1 s the interval between two similar complexes is always 0.84 sec The ventricular rhythm is then rapid and regular with a rate of 142 beats per minute

The QRS interval of the leftward ÂQRS beats measures 0.17 sec in Leads I and II and looks much narrower in Lead III The QRS interval of the rightward ÂQRS beats also measures 0.17 sec. on Lead I but looks narrower in Lead II

13 cases of bidirectional tachycardia Table I summarizes the main facts of 13 cases of BT In all of them the electrocardiographic features were remarkably similar to those of the case in Fig 1 (1) There was an RBBB pattern in each one of the 12 cases in which precordial leads had been recorded (2) In each of the 13 cases the ÂQRS of the leftward QRS complexes pointed around −60 degrees, and that of the rightward beats, almost uniformly at +120 degrees. (3) The ventricular rhythm was regular except in Cases 2 and 3 in which although there was a minimal difference between successive different complexes there was none between successive similar c... (4) The QRS width was less than ... in 3 cases of 0.12 sec in 6 and gr... 0.12 sec in 4 (5) The ventric... ranged between 140 and 180 b... minute except in one case in whic... 14 (6) In 7 cases no P wave was ...

Table I 13 cases of bidirectional tachycardia

Case no	QRS interval (sec)	ÂQRS: QRS with LAD (degrees)	ÂQRS: QRS with RAD (degrees)	R R interval (sec): LAD RAD	R R interval (sec): RAD LAD	R R interval (sec): LAD LAD	R R interval (sec): RAD RAD	Precordial leads	P wave and atrial rate
1	<0 12	−60	+120	0 35	0 35	0 70	0 70	RBBB	No
2	>0 12	−80	+120	0 39	0 43	0 80	0 80	RBBB	Doubtful
3	<0 12	−60	+120	0 31	0 32	0 63	0 62	RBBB	No
4	>0 12	−80	+120	0 42	0 42	0 84	0 84	RBBB	Doubtful
5	0 12	−60	+120	0 34	0 34	0 68	0 68	RBBB	Yes 270
6	>0 12	−60	+120	0 34	0 34	0 68	0 68	RBBB	No
7	<0 12	−80	+120	0 32	0 32	0 64	0 64	RBBB	Yes 75
8	0 12	−60	+120	0 38	0 38	0 76	0 76	RBBB	Yes 125-130
9	0 12	−80	+120	0 42	0 42	0 84	0 84	RBBB	A.F
10	0 12	−45	+120	0 38	0 38	0 76	0 76	RBBB	No
11	>0 12	−60	+120	0 40	0 40	0 80	0 80	RBBB	A.F
12	0 12	−60	+120	0 28	0 28	0 56	0 56	RBBB	Yes
13	0 12	−60	+120	0 36	0 36	0 72	0 72	RBBB	No

Abbreviations A.F Atrial fibrillation LAD left axis deviation RAD, right axis deviation.

(2 of these with atrial fibrillation) in 2 its presence was doubtful and in 4 P waves dissociated from ventricular activity were recognized

47 cases of bidirectional tachycardia from the literature In 47 cases of BT reported by different authors[illegible] we found again that (1) There was a RBBB pattern in each one of 12 cases in which precordial leads were reproduced[illegible] (2) the QRS direction whenever the number of leads rendered possible its determination was always around −60 and +120 degrees for each one of the two types of ventricular complexes (3) the rhythm was usually regular When it was not the R R interval changed no more than 0 04 sec between successive cycles and in such cases, the R R intervals separating successive leftward or "rightward QRS complexes were always equal indicating that both types of complexes have the same rate.

Summary of the preceding observations Each one of our 13 cases of BT as well as most of the 47 cases reviewed from the literature showed the existence of three essential features (1) alternant ventricular complexes with an ÂQRS pointing around −60 or +120 degrees (with a pattern of LAH or LPH respectively) ( ) an RBBB pattern in every beat (3) a regular rhythm. We may then conclude that *BT is a perfectly or almost perfectly regular alternation of two types of beats one of them showing a pattern of RBBB with LAH the other a pattern of RBBB with LPH*

Irregularities in the diastolic intervals and atypical QRS forms may occur however at the initial and terminal boundaries of the episodes.[3] Accordingly BT should be considered (1) when short bouts of bidirectional beats with an RBBB pattern occur even if the diastolic intervals are not perfectly regular and even if the ÂQRS of some of the ventricular complexes does not reach the direction usually seen in typical stabilized cases (Fig 2) (2) when during a unidirectional tachycardia with an RBBB pattern and an ÂQRS greatly deviated to the left (or to the right) some beats exhibit distinct electrical opponency or even intermediate deviations (not due to fusion beats) (Fig 3) Each of these two variants should be considered as heralding typical BT

The existence of an RBBB pattern in every beat and in every case should be considered as one of the most significant features of the electrocardiographic picture of BT Had this been known before many hypotheses on the mechanism of BT would

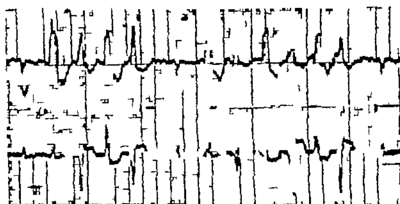


Fig. 2. Two isolated bouts of bidirectional tachycardia (V and Lead III simultaneously recorded). In each one, the first beat shows pattern of pure RBBB the second, of RBBB with LAH and the third, of RBBB with LPH. There are changes in the degree of each hemi bloc and perhaps too in the degree of the RBBB.



Fig. 3. During a "unidirectional" supraventricular tachycardia with a QRS pattern of RBBB with LAH, there are changes in the degree of the LAH and also some beats with patter of LPH. Premonitory changes of a typical bidirectional tachycardia.

have been avoided. However because of reasons given later in this paper an exceptional case with alternant opponency and no RBBB pattern might exist.

The QRS width is not such a consequential element within the picture of BT for as we have seen it may be higher or lower than 0.12 sec. although in most of the cases it is of 0.12 sec. or more. However the existence of cases with a relatively narrow QRS complex should be covered by any comprehensive hypothesis on the mechanism of the arrhythmia.

Previous hypotheses

For a critical review the best known hypothesis may be listed in three groups, according to the assumed site of origin of the responsible pacemaker or pacemakers (1) ventricular origin (2) supraventricular origin (3) mixed origin.

Ventricular origin. Within this group the hypothesis attaining the greatest success was the one assuming the existence of two independent pacemakers, one in each ventricle discharging alternately. This hypothesis was first stated by Levy and Lewis,[12] who reported instances of BT elicited in cats through inhalation of chloroform vapor. In 1923 Felberbaum[13] reported a clinical case and mentioned the same hypothesis.

The hypothesis of a circus movement advanced by Luten[14] and by Lewis,[15] is

mentioned by Gallavardin, who described it as "a circus movement within the ventricles similar to atrial flutter." Subsequently, Marvin[36] and Palmer and White[73] suggested the existence of a "double circus movement" to explain an assumed alternation in the duration of diastoles.

Di Mateo and associates, noticing in one case that all the beats exhibited an RBBB pattern in the chest leads, concluded that BT could not be caused by a pacemaker in each ventricle and suggested that both were in the left ventricle.

Finally, Katz and Pick[8] postulated a single ventricular pacemaker somewhere below the bifurcation of the bundle of His and equidistant from both bundle branches, with alternant block in each of them.

Supraventricular origin. In this group the most popular hypothesis is the one propounded by Felberbaum,[22] who suggested that the impulses from a single pacemaker, probably located in the A-V node or in the main bundle, are alternately conducted through the right and left bundle branches.

Other hypotheses may be considered as variations from the preceding one, for they also attribute BT to a supraventricular pacemaker and to intraventricular conduction disturbances. Among these, the following may be mentioned: (1) Katz and Pick suggested the existence of a supraventricular pacemaker with RBBB alternately changing its degree. (2) Spang[44] offered a supraventricular pacemaker with 3:2 exit block as an explanation for the alternation of the diastolic intervals in some cases. (3) Chevalier conjectured BT was a nodal tachycardia with aberrant ventricular conduction and some sort of variable antegrade block. (4) Rakita and associates[13] suggested it was a nodal disturbance producing an alternating pattern of RBBB and LBBB due to a regional distribution in the ventricles of the conduction fibers and to the functional isolation of such groups of fibers from one another. (5) Sepaha and associates[16] hypothesized it was two nodal foci discharging alternately. (6) Finally, Pick and associates[17] in a report on nodal tachycardias with block decidedly include BT with "regular rate and rhythm" in them, attributing the opponency of the ventricular complexes to a functional disorder of conduction developed in the ventricles alternately affecting the way of propagation of the impulses.

Mixed origin. Zimdahl and associates[8] suggest the existence of two pacemakers, one in the A-V node and the other in one of the ventricles, discharging alternately. In order to support this, they refer to a case of BT in which carotid sinus stimulation suppressed one of the two types of ventricular complexes but not the other, thus halving the heart rate.

A new hypothesis

There are two fundamental reasons why the above quoted authors could not solve the problem. First, they did not possess all the necessary information. Actually, they did not know that in every case all the ventricular complexes have a RBBB pattern and they also ignored the fact that the complexes of BT have two definite ÂQRS directions. Thus, it is obvious that no hypothesis skipping those essential facts could have ever been correct. However, even if the information had been complete, it would also have been very difficult to accomplish a satisfactory solution. The second reason is of a doctrinal nature. Every author who tried to solve the problem of the mechanism of BT believed that the intraventricular conduction system is bifascicular and always behaves as such. With this assumption the problem could never be solved. On the other hand, if we just keep in mind that the conduction system may operate as trifascicular, the mechanism of BT becomes much more simple, as we shall try to demonstrate now.

A good hypothesis on the mechanism of BT should give an answer to the following questions: (1) Why do the opponent beats have always an ÂQRS around either −60 or +120 degrees? (2) Why do both of them have constantly a RBBB pattern? (3) Why is the rhythm perfectly regular in most of the cases? (4) Why do many cases respond to vagal stimulation? According to previous studies,[24] the first two questions may be reduced to a single one: Why do the opponent beats always exhibit a pattern either of RBBB with LAH or of RBBB with LPH? All the above questions are appropriately answered with the following assumption: *BT is a supraventricular tachycardia with permanent aberrant conduction*

in the right bundle branch and alternant aberrant conduction in the two divisions of the left bundle branch

The fact that the bidirectional complexes always and uniformly exhibit the same two patterns of RBBB with LAH and RBBB with LPH reduces the possible mechanisms of BT to only two either two pacemakers, one in the anterior and the other in the posterior wall of the left ventricle, discharging regularly and alternately (which is very unlikely) or a single supraventricular pacemaker eliciting a pattern of permanent RBBB and of alternant LAH and LPH due to aberrant ventricular conduction of the rapid-rate impulses of this pacemaker To support this statement the following may be mentioned We have reported elsewhere[34] numerous examples of supraventricular premature beats with aberrant ventricular conduction whose electrocardiographic pattern was either of RBBB with LAH or of RBBB with LPH the same type of beats as in BT Therefore if these types of ventricular aberration may occur in isolated premature beats, there is no reason why they should not occur regularly or periodically during episodes of supraventricular tachycardia. This also explains why the beats of BT may have a QRS interval longer or shorter than 0 12 sec. the latter occurring when aberration within the right bundle branch is of a moderate degree so as to produce a pattern of incomplete RBBB It also explains why in the beginning of some cases of BT when a steady state is progressively reached the ÂQRS deviations may be intermediate between the typical extremes. It also explains the cases of "unidirectional supraventricular tachycardia (with a pattern of LAH) which changes to bidirectional without significant changes in rate[17] or when the rate increases slightly and progressively it keeps the ÂQRS direction of the unidirectional rhythm in one of the two types of QRS.

Perhaps the most difficult and crucial point of the mechanism of BT is to explain the alternant LAH and LPH We have previously reported[34] that aberrant ventricular conduction of supraventricular premature beat eliciting a pattern of LAH and LPH (alone or combined with RBBB) occurs not unfrequently in the same patient. Thus the cycle may start in the following way Inasmuch as the right bundle branch is the most labile of the main three terminal fascicles of the intraventricular conduction system and the one having the longest Q-T interval [34] it can be expected that from the onset of the supraventricular tachycardia, the first beat and then all the following should be conducted with delay or blocked in that bundle branch producing a constant pattern of RBBB Since the anterior division of the left bundle branch is the fascicle which follows in order of vulnerability and has a longer Q T interval than that of the posterior division [34] it is not surprising that also from the beginning of the tachycardia a beat should be blocked in the anterior division (at the same time as that in the right bundle branch) If in such a beat the posterior division has conducted with normal or only subnormal speed in such a way that the impulse arrives too early to activate retrogradely the anterior division (very likely since both fascicles belong to the same ventricle) it is easy to imagine that in the next beat the anterior division will be better recovered than the posterior and conduction will be blocked in the latter but will take place through the former The cycle could thus be indefinitely repeated.

The great majority of supraventricular tachycardias display normal intraventricular conduction A small group show aberrant conduction usually of the RBBB type, either pure or with LAH and sometimes of the LBBB type Only a very small or insignificant number of these are bidirectional with aberration of the RBBB type plus alternant LAH and LPH with evidence of impaired conduction in the main three terminal fascicles of the intraventricular conduction system All this suggests is that for BT to occur it is necessary to have some damage to the conduction system in addition to a supraventricular tachycardia of rapid enough rate. It is difficult to prove this assumption but diffuse myocardial damage and a strong digitalis effect are almost always present whenever the arrhythmia occurs.

In the overwhelming majority of the cases, BT occurs in patients with severe myocardial damage and in advanced heart failure whatever the etiology It is con-

ceivable, under such conditions, that the right bundle branch and the two divisions of the left may share the precarious metabolic conditions affecting the whole heart. This, in turn, may prompt or facilitate (if at the same time a supraventricular tachycardia of rapid enough rate supervenes) the emergence of the paroxysmal intraventricular conduction disturbances which characterize BT.

The decisive role of digitalis in the production of BT has long been stressed and is supported by the following facts. (1) Almost every case of BT from the literature and 12 of our 13 cases were on digitalis. (2) The withdrawal of digitalis is an essential measure for the treatment of the arrhythmia. (3) In clinical cases, the intravenous *injection of acetyl strophanthidin* or ouabain made BT appear in a few minutes.[1] (4) BT has been induced in dogs by injecting acetyl strophanthidin into the A-V node[illegible] or into the veins.[illegible] However, it also seems indubitable that the drug requires some predisposition on the part of the patient for the BT to occur. Such predisposition is the severe cardiac condition of the patient, which motivates the administration of the drug.

Digitalis may provoke BT through a two-fold effect: first, because it may directly trigger off the supraventricular tachycardia; second, because it may depress conduction and thus favor the characteristic intraventricular conduction disturbances. We have more than enough clinical evidence to prove the first effect.[illegible] Besides, under experimental conditions, digitalis may frankly increase the rate of automatic discharge in the A-V node and in the Purkinje tissue from the bundle of His onward.[illegible] It is less known that digitalis may favor the occurrence of intraventricular conduction disturbances. However, it has been proven beyond any doubt that digitalis may depress conduction in the fibers of the A-V node and in the Purkinje fibers up to the point of complete unresponsiveness, while the common myocardial fibers still keep their normal excitability.[illegible] These observations are significant in the present context, for under clinical conditions as the ones commented upon, digitalis could very well depress excitability in the main three terminal fascicles of the intraventricular conduction system to such an extent as to allow the occurrence of the characteristic paroxysmal or "functional" conduction disturbances of BT. This depression would not be so important that bundle branch block would occur with normal or slow heart rates, but it would be enough so that this type of conduction disturbance would show up if the rate is rapid, as in the presence of the supraventricular tachycardia provoked by the same drug. In an unpublished case[illegible] a very large amount of digitalis taken involuntarily by a normal subject, produced transient RBBB even with a slow heart rate.

Summary and conclusions

BT is a supraventricular tachycardia *with fixed aberrant conduction in the right* bundle branch and alternant aberrant conduction in the two divisions of the left. This new hypothesis accounts satisfactorily for the four essential features of this arrhythmia: the regularity of its rhythm, its eventual response to vagal stimulation, the presence of a RBBB pattern in every beat, and the existence of a pattern of alternant LAH and LPH. We may also say that BT is, in the final event, some sort of acute or *paroxysmal trifascicular block* related from an electrocardiographic point of view to the trifascicular blocks recently reported by our same group.[illegible] Because it is a trifascicular block, some variants in the regular pattern of BT are to be expected. For instance, should the conduction impairment become more important in the three fascicles, A-V conduction disturbances also ought to appear, as actually seems to occur in the beginning or in the end of some paroxysms of BT. In addition, should the conduction disturbance be less important within the right bundle branch, the beats of BT might occur without RBBB as a form of "pure" alternant LAH and LPH, or eventually beats with a LBBB pattern might also occur. Although we cannot exemplify those situations, the hypothesis predicts them and we hope they will be seen in future cases when looked for. The reason why they can only rarely occur is because the right bundle branch is the most labile of the three terminal fascicles of the conduction system. The fact that the conduction disturbance in the right bundle

branch is more important than in the two divisions of the left is decisive in the steadiness of the electrocardiographic pattern of BT

BT occurs in subjects with very diseased hearts and almost invariably in the presence of digitalis. These circumstances trigger the supraventricular tachycardia and spoil the conduction system enough for the conduction disturbances which characterize the arrhythmia to occur particularly because the rapid heart rate favors those conduction disturbances to become manifest.

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False-positive exercise test in the presence of the Wolff Parkinson White syndrome

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It has been approximately 38 years since the Wolff Parkinson White syndrome (WPW or pre-excitation) was described However the incidence of incorrect electrocardiographic interpretation related to this entity remains inappropriately high Wolff Parkinson and White[1] estimated that one third of the cases are incorrectly diagnosed by the physicians who first see them Incorrect diagnoses of myocardial infarction bundle branch block ventricular hypertrophies, and ventricular tachycardia have been made This report emphasizes that a false-positive exercise test often occurs in the presence of the WPW syndrome accounting for the mistaken diagnosis of ischemic heart disease

A double two-step Master s exercise test was performed on 23 patients between the ages of 17 and 59 with the WPW syndrome by a method previously described These patients were asymptomatic and had no evidence of heart disease.

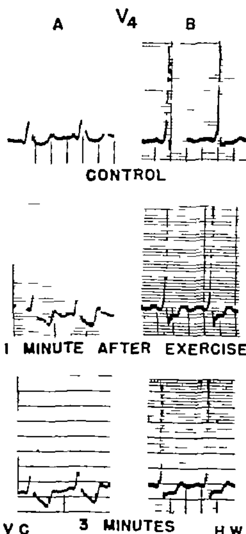


Fig. 1 T patients (A and B) 17 years and 29 years of age, respectively with the WPW drome. After exercise right angle S-T depression with T-wave inversion occurred

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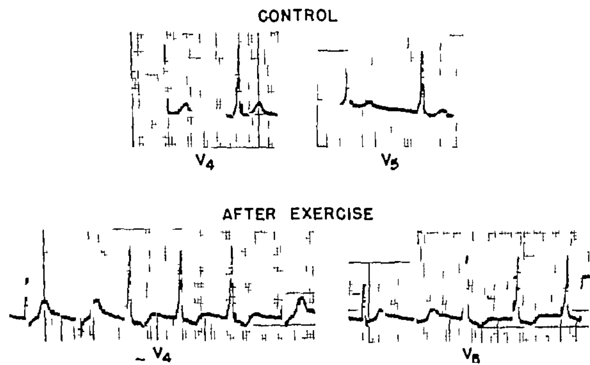


Fig. 2. A 30-year-old patient with the WPW syndrome. After exercise there is intermittent normal and WPW conduction. During the WPW conduction, S-T depression with inverted T waves can be seen which did not occur in the normal conducted beats.

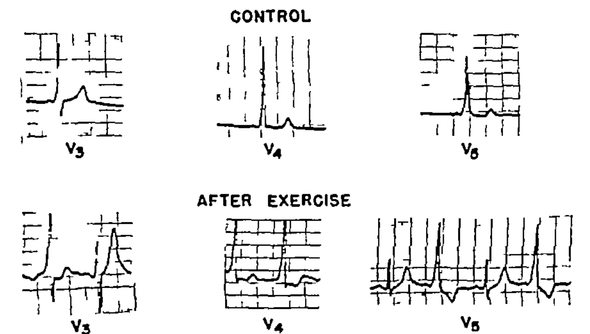


Fig. 3. A 42 year-old p tie t with WPW ynd e. Note in the V and V leads after exercise that there is alternating WPW and r rmal conduction, exercise changes occurring only in the WPW complexes.

Results

Twenty of these patients had a positive double Master's exercise test characterized by right angle S-T segment depression of 1 mm. or more with or without inversion of the T waves (Fig. 1). Figs. 2 and 3 depict two patients with intermittent WPW and normal conduction occurring after exercise with positive exercise changes seen only during the WPW conduction.

Discussion

Today many forms of electrocardiographic exercise tests (Master's,[3] near maximum, or maximum exercise[4]) are being performed especially on patients with atypical chest pain. Regardless of the type of exercise test we must be aware of false positive changes. Such false-positive tests have been known to occur in the presence of digitalis, bundle branch block, hypertrophies, healed pericarditis, and autonomic changes. Lamb described one subject with multiple variation of WPW conduction who had a false-positive exercise test. In the presence of the WPW syndrome positive exercise changes frequently occur and are probably secondary changes as are seen after exercise in patients with bundle branch block. These are secondary ST-T changes opposite in direction and proportionate in magnitude to the main deflection of the QRS complex in area. Often physicians do not recognize the WPW syndrome in the resting tracing and the error is compounded with a positive Master's exercise test.

Summary

Twenty-three patients with electrocardiographic findings typical of the WPW syndrome but no evidence of heart disease were exercised utilizing a double two-step Master's exercise test. Twenty of these had positive changes. In the presence of the WPW syndrome the electrocardiographic exercise test is of no value in view of the frequent false-positive changes.

I wish to thank Dr. J. N. Berry, Atlanta, Ga., and Dr. J. A. Morrish, Bradenton, Fla., for each allowing me to include one of their patients in this study.

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Potassium loss with thiazide therapy

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Thirty to 40 per cent of hypertensive patients treated with thiazides have a lowering of serum potassium to below 3.5 mEq. per liter. Although short-term balance studies have demonstrated a urinary loss of potassium with thiazide administration,[1-3] potassium loss with long-term therapy as a direct cause of a lowered serum potassium has been questioned, and exchangeable potassium determinations have been reported as showing no significant potassium loss.[4] In the present study, metabolic balance methods were used in nonedematous hospitalized patients to evaluate the potassium loss associated with thiazide administration.

Patient selection and methods

Eight men with normal renal function as evidenced by normal serum creatinine and blood urea nitrogen levels and with mild to moderate uncomplicated essential hypertension who had been treated with hydrochlorothiazide as outpatients were hospitalized and studied on the metabolic ward. All patients were instructed to stop medication 2 weeks prior to hospitalization. On the initial day of hospitalization the dietitian interviewed the patient and composed a diet which was held stationary throughout the study. This diet contained between 80 to 90 mEq. of potassium (average 86 mEq.) and between 90 to 110 mEq. of sodium per day (average 103 mEq.). All liquids were measured and all solids were weighed. The diets were prepared in the kitchen of the metabolic ward. The sodium and potassium content were ascertained from tables compiled from previous photometric analyses and checked by analysis of duplicate diets. The standard deviations of sodium and potassium in the diets as ascertained by this analysis were ± 2.8 mEq. for sodium and ± 2.0 mEq. for potassium.

Because there is a significant insensible loss of sodium and potassium,[7] statistical comparison between the actual diet content and the loss of these electrolytes in urine plus stool would introduce an error. Therefore, the statistical comparisons were made between the urine plus stool loss of sodium and potassium during the last 4 days of the control period and for sequential periods during the treatment period. (See "Statistical methods.")

There was a hospital control period that ranged from 7 to 14 days (average 11.3

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days) Subsequently 50 mg of hydrochlorothiazide three times daily were prescribed for 14 to 67 consecutive days (average 33 days) Twenty four hour urine specimens and all stools were collected Sodium and potassium content of the 24 hour urine specimens and of 7 day ashed stool collections were determined by flame photometry Serum and urine creatinine were measured by the Folin Wu method In 5 of the 8 patients 24 hour urine-aldosterone excretion rate was determined by the method of Kliman and Peterson Plasma pH pCO and HCO⁻ were measured by the method of Astrup and associates[9] during the control and treatment periods.

Statistical methods

To guard against possible constant biases in the nominal potassium and sodium intakes, the nominal intakes were corrected to zero values determined from in balance control periods. Fig 1 shows that control period balance was attained on the sixth day of hospitalization

Following the initiation of hydrochlorothiazide treatment, extreme transient disturbance of ion balance lasted for 7 days, after which stable treatment periods were defined. For each patient t tests were performed for changes of distribution of measured variables between the in balance control period and the stable treatment period

For each measured variable the hypothesis of each patient's stable treatment period mean μ equal to his control period mean μ_c was tested within the hypothesis of a linear regression of μ on μ_c with the same coefficients for each patient. An F statistic was obtained by treating each patient's averages as paired observations

Results

Fig 1 depicts the average potassium and sodium excretion in urine plus stool for the group of 8 patients during the pretreatment control period From the sixth day of this period it is evident that the group was in balance A dose of 150 mg of hydrochlorothiazide daily resulted in a loss of sodium during the first 3 days of therapy followed by a period of sodium retention from the fourth to eighth day of treatment The total sodium excretion when averaged was not significantly different from the control levels. Potassium loss was also most marked during the first 3 days of hydrochlorothiazide administration but in contrast to sodium there was no subsequent potassium retention Cumulative net potassium losses are shown in Fig 2 Serum potassium dropped from an average control level of 4 1 to 3 2 mEq per liter by the end of the

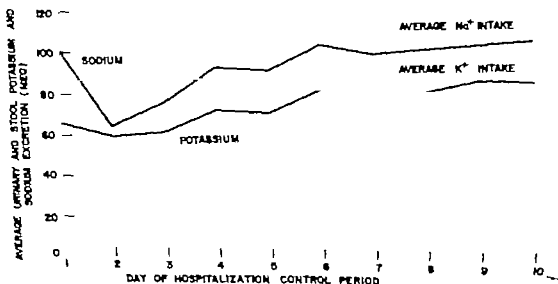


Fig 1 Control period urinary urine plus stool sodium and potassium excretion per 24 h the group of 8 patients studied.

*Table I Local time averages of parameters averaged (unweighted) over patients**

Time	No. of patients	K loss (mEq./day)	Serum K (mEq./L.)	Na loss (mEq./day)	Serum Na (mEq./L.)
In-balance control period (variable length)	8	0 0 (0 0)	4 1 (0 2)	0 0 (0 0)	141 (4)
Treatment					
Period 1 (3 days)	8	38 2 (16 6)	3 7 (0 5)	68 6 (37 5)	139 (4)
Period 2 (4 days)	8	28 2 (20 1)	3 2 (0 4)	−22 5 (22 5)	140 (2)
Period 3 (7 days)	8	3 3 (5 6)	3 2 (0 3)	−11 3 (19 1)	140 (2)
Period 4 (7 days)	7	2 7 (10 5)	3 4 (0 2)	−3 3 (18 5)	141 (5)
Period 5 (7 days)	6	5 2 (3 7)	3 4 (0 2)	−6 4 (24 3)	140 (3)
Period 6 (7 days)	3	4 9 (3 3)	3 2 (0 1)	7 2 (9 4)	142 (2)
Period 7 (7 days)	3	−1 6 (2 2)	3 1 (0 3)	12 7 (20 5)	142 (2)
Periods 3–7 (variable length)	8	3 4 (5 6)	3 3 (0 3)	−7 3 (18 5)	141 (3)

*Standard deviations between patients appear in parenthesis.

*Table II Comparisons paired by patient of stable treatment period and in-balance control period values**

Variable	Serum K	Serum Na	Aldosterone excretion	Blood pH	Blood HCO_3^-	Blood pCO_2	Blood pressure (10 min standing)		Body weight
							Systolic	Diastolic	
F_{max} statistic	40 3 (005)	3 5 (10)	144 2 (005)	26 3 (005)	22 0 (005)	16 9 (005)	18 2 (005)	9 6 (01)	35 2 (005)
Degree of freedom m	2 6	2 6	2 6	2 6	2 6	2 6	2 6	2 6	2 6

*Values presented are the F ratios of control versus treatment period data. The F-statistic significance levels appear in parenthesis.

first week of therapy and remained near this level The serum and urinary creatinine levels did not change significantly In Table I the pertinent data are averaged and presented for the control and study periods

A weight loss that averaged 1.5 kg for the 8 patients studied occurred within the first 3 days of hydrochlorothiazide therapy This was associated with an increased urine volume and was attributed to fluid loss. There was no further significant sustained weight loss during the remainder of the study

Aldosterone excretion rose from an average control level of 10 7 to 20 8 μg per day on the fourth to eighth day of the treat

Aldosterone excretion (μg/24 hr)	Blood pH	Blood HCO	Blood pCO (mm Hg)	B.P (mm Hg) (10 m standing) Systolic	Diastolic	Body wt. (Kg)
10 7	7 438	26 2	37 4	142	93	83 3
(2 0)	(022)	(3 3)	(7 0)	(33)	(19)	(18 8)
13 0	7 427	23 8	37 6	137	92	81 8
—	(034)	(2 0)	(5 2)	(33)	(21)	(18 3)
20 8	7 460	29 0	41 9	125	87	80 7
(8 4)	(021)	(1 8)	(0 5)	(34)	(18)	(18 2)
18 6	7 479	29 5	40 9	125	85	80 4
(1 2)	(020)	(2 4)	(2 8)	(30)	(17)	(18 1)
17 7	7 465	28 5	41 4	125	86	78 4
—	(022)	(3 0)	(4 4)	(33)	(19)	(18 4)
21 6	7 468	29 4	43 5	127	83	80 4
(0 4)	(026)	(2 5)	(4 9)	(33)	(20)	(18 3)
—	7 458	28 5	42 3	111	73	67 6
	(033)	(2 0)	(5 4)	(7)	(8)	(5 2)
—	7 448	29 6	44 8	106	69	67 5
	(031)	(1 1)	(5 3)	(12)	(13)	(5 3)
19 6	7 472	28 7	41 1	124	85	80 1
(1 4)	(018)	(2 5)	(3 8)	(30)	(17)	(17 9)

Table III *Correlation coefficients (Pearson s r) and confidence limits of cumulative sodium and potassium losses with blood pH and bicarbonate levels and aldosterone excretion rates**

Variables	Blood pH	Blood HCO_3	Aldosterone excretion
Potassium loss			
Pearson	51	54	71
Confidence interval (95)	(27 68)	(33 72)	(28 88)
Sodium loss			
Pearson	− 19	00	10
Confidence interval (95)	(− 45 08)	(− 28 28)	(− 42, 57)

*There are positive correlations with potassium loss and increased blood pH, and blood bicarbonate and aldosterone excretion. There are no similar correlations evident with sodium balance figures.

ment period and did not change significantly during the remainder of the study This represents a slight but statistically significant increase in aldosterone excretion. The individual aldosterone excretion rates are presented in graph form in Fig 3 The blood pH pCO and bicarbonate levels also showed a slight but statistically significant increase with hydrochlorothiazide therapy Table II presents the levels of statistical significance of the control period versus the treatment period data.

Discussion

The average cumulative potassium loss with hydrochlorothiazide for the group of

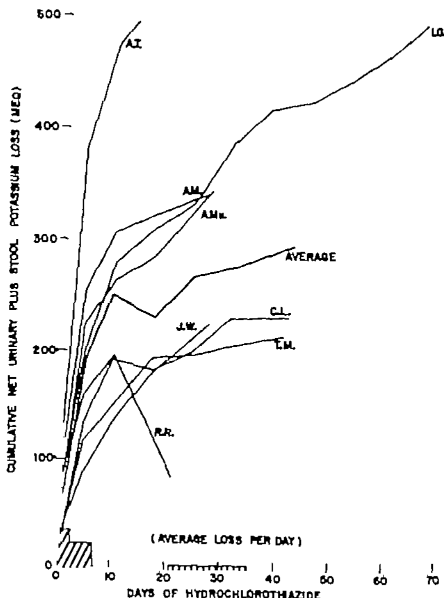


Fig. 2. Cumulative net potassium loss associated with administration of 150 mg. per day of hydrochlorothiazide

8 patients studied was 295 mEq (Fig. 2). There was no evidence of self-correction of the potassium loss during hydrochlorothiazide therapy. Significant sodium loss, however, occurred only during the first 3 days of therapy with subsequent sodium retention and at least partial correction of the initial loss. The aldosterone excretory rate was in the low normal range for each patient during the control period. The aldosterone excretory rate increased with therapy and presumptively this increase was triggered by the initial sodium loss that resulted from hydrochlorothiazide administration. The continuation of the urinary potassium loss during the period that sodium was being conserved may be a result of this mild aldosteronism. The correlation coefficients between amount of sodium excretion and aldosterone excretion and between amounts of potassium excretion and aldosterone are presented in Table III.

The control serum potassium levels exceeded 3.8 mEq. per liter in each patient. There was a statistically significant decrease in serum potassium level with hydrochlorothiazide therapy, and this decrease was sustained. Individual serum

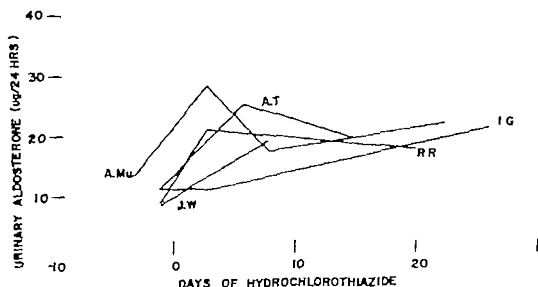


Fig 3 Aldosterone excretory levels before and during hydrochlorothiazide therapy

potassium levels were a poor index of the total potassium loss but the 2 patients that had a serum level below 3 0 mEq per liter did have the largest cumulative potassium loss.

The slight but statistically significant increase in blood pH pCO_2, and bicarbonate levels also correlated fairly well with the potassium loss but not with the state of the sodium balance (Table III)

Summary

Nonedematous patients with essential hypertension were studied by metabolic techniques while hospitalized Hydrochlorothiazide therapy resulted in a transient natriuresis which subsequently was partially compensated for by renal sodium retention. Urinary potassium loss accompanied the natriuresis and continued during the period of the compensatory renal retention. Evidence was presented that indicate a slight but statistically significant increase in aldosterone excretion during the period of hydrochlorothiazide therap

We are grateful for the technical assistance of Mrs. Catherine Nobe, a technologist t the linical pharmacology laboratory

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The use of amiloride in potassium depletion before cardiac surgery

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The increased incidence of digitalis toxicity[1,2] has been attributed to electrolyte disturbances which can follow treatment with potent oral diuretics. Patients on prolonged diuretic therapy with depletion of total body potassium[3] are particularly vulnerable. This hazard assumes even greater importance in patients who subsequently require open heart surgery. During heart lung bypass, the further potassium depletion that often occurs may aggravate the tendency to postoperative arrhythmias.

The two methods most commonly advocated to prevent potassium loss due to diuretics are the use of oral potassium supplements and the administration of the potassium-sparing diuretics, spironolactone and triamterene. Neither method has proved entirely satisfactory. We therefore studied the effectiveness of the more potent potassium conserving agent amiloride hydrochloride[4,5] in reducing potassium loss. This drug was used in combination with the potent diuretic furosemide. The total body potassium depletion was measured with ^{40}K at the start of the trial and balance studies were used to evaluate the urinary potassium losses that occurred.

Subjects and methods

Ten patients with valvular heart disease were selected for study from the Cardiological Wards of Greenlane Hospital Auckland. Their salient clinical features including details of previous diuretic treatment, are presented in Table I. All cases had been in congestive heart failure but this was controlled by maintenance doses of diuretics and digoxin. None was markedly edematous. The serum potassium levels were within the normal range in all cases, and all patients except one (Patient F6) subsequently underwent corrective surgery on heart lung bypass.

The patients were placed on diets that provided 70 mEq of potassium and 22 mEq of sodium daily with an unrestricted fluid intake. Two patients (F5 and F6) took 50 mEq of sodium daily. Previous diuretics and potassium supplements were stopped at the start of the trial but a fixed dose of digoxin was continued. Furosemide, 80 mg daily (40 mg at 7 A.M. and 40 mg at 1 P.M.) was started in all cases except in two patients (M1 and M12) who because of their serious clinical condition were given 120 mg daily (80 mg at 7 A.M. and 40 mg at 1 P.M.). Following a two

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Table I. Summary of clinical data

Patient (sex and no.)	*Age*	*Diagnosis*	*Previous daily diuretic therapy*	*Duration of therapy (months)*
F1	23	Mitral stenosis	Furosemide, 80 mg; spironolactone, 100 mg; potassium supplement, 20 mEq	2
F2	24	Multivalvular rheumatic heart disease	Cyclopenthiazide, 0.5 mg; potassium supplement, 13 mEq	12
F3	28	Residual pulmonary stenosis following repair of tetralogy of Fallot	Furosemide, 40 mg; spironolactone, 100 mg	1
F4	33	Multivalvular rheumatic heart disease	Furosemide, 40 mg; potassium supplement, 20 mEq	9
F5	45	Postmitral valvotomy with congestive heart failure	Furosemide, 80 mg; potassium supplement, 40 mEq	6
F6	64	Calcific aortic stenosis	Furosemide, 40 mg; spironolactone, 100 mg; potassium supplement, 20 mEq	2
M1	34	Rheumatic mitral incompetence	Furosemide, 120 mg; spironolactone, 100 mg; potassium supplement, 40 mEq	6
M2	43	Multivalvular rheumatic heart disease	Furosemide, 80 mg; spironolactone, 100 mg; potassium supplement, 20 mEq	3
M3	52	Multivalvular rheumatic heart disease	Furosemide, 80 mg; spironolactone, 150 mg	3
M4	54	Mitral stenosis	Furosemide, 60 mg; potassium supplement, 20 mEq	6

day equilibration period, control data on furosemide was obtained for 4 days. This was followed by an 8 day period during which amiloride hydrochloride (10 mg at 7 A.M. and 10 mg at 1 P.M.) was given in combination with furosemide. Both diuretics were administered orally.

Twenty-four hour urine specimens were obtained daily for the estimation of sodium, potassium, and the endogenous creatinine excretion. Samples of blood for hemoglobin, hematocrit, white blood cell and platelet counts and serum for electrolytes, urea, creatinine, fasting sugar, uric acid, and tests of liver function were taken before and immediately after each phase of the investigation. The blood pressure and weight were recorded daily in all patients and clinical assessment was made at frequent intervals during the study.

The serum sodium, potassium, bicarbonate, urea, and the serum and urinary creatinine were analyzed with Technicon Auto-Analyser and the urinary sodium and potassium with an internal standard flame photometer.

Total exchangeable potassium (K_e) was estimated at the beginning and at the end of the 2 week study period using the ^{42}K dilution principle. On the first morning of the study period 100 ml. of water containing an accurately measured quantity of ^{42}K (100 to 250 μc) was taken orally by each subject in the fasting state. Urine was collected for the next 24 hours, following which five hourly spot urinary collections were made. Urinary volumes were recorded and aliquots of each period taken for counting of ^{42}K and chemical measurement of ^{39}K.

Urine and a dilute standard prepared from the oral ^{42}K dose were both counted in volumes of 6 ml. in plastic tubes in a Packard twin-channel "Autogamma" spectrometer. Sample and background counts were adjusted to ensure counting errors of less than ±2 per cent. All counts were corrected for radioactive decay using standard tables. Chemical ^{39}K estimation by flame photometry was performed in duplicate on each of two aliquots of every urinary specimen.

Table II Mean diuretic response and changes in endogenous creatinine clearance in patients on furosemide (Fr) for 4 days and on furosemide and amiloride (Am) for 8 days

Patient (sex and)	Weight (kg)			Urinary volume (ml. per 24 hours)		Urinary sodium (mEq per 24 hours)		Urinary potassium (mEq per 24 hours)		Endogenous creatinine clearance (ml per minute)	
	Initial	F	F + Am	F	F + Am	F	F + Am	F	Fr + Am	Fr	Fr + Am
F1	51	50	49	1778	1837	12	58	82	59	56	55
F2	49	47	47	2060	1261	104	78	58	38	44	48
F3	38	38	38	1208	1434	12	32	43	25	58	35
F4	53	52 5	50	1763	1615	21	39	59	31	67	70
F5	88	83	82	2685	1895	59	66	62	32	70	69
F6	55	55	51	990	1157	18	47	40	29	43	35
M1	57	57	54	1650	1981	26	73	59	49	63	60
M2	90	87.5	87	2142	1810	17	40	96	57	86	82
M3	92	91	85	1488	1872	30	136	77	55	57	70
M4	65 5	65	63	1580	1815	23	49	98	62	65	62
Mean	—	—	—	1734	1678	32.2	61.8	67 4	43 7	60 9	58.6

Since there is evidence[1] that equilibration between ^{42}K and body potassium is not always complete after 24 hours, the procedure of Flear and associates was followed in checking the trend of successive hourly K_e estimations after the 24 hour equilibration period. All but two of the subjects (F5 and M13) were lean and this was confirmed by fat fold measurements. The values for K were therefore not corrected to lean body mass.

Results

Urinary and serum electrolyte change The mean diuretic response to furosemide alone (80 to 120 mg) and in combination with 20 mg daily of amiloride is shown in Table II and Fig 1. With the exception of one case the natriuresis induced by furosemide was enhanced by amiloride without a consistent increase in the urinary volume. The patient (F2) whose sodium output decreased showed a brisk response to 80 mg of furosemide and became mildly depleted of sodium before amiloride was added. In one patient (M13) there was a daily stepwise increase in sodium excretion which reached the maximal figure of 250 mEq on the eighth day of the combined regime. For the whole group the sodium excretion was increased 92 per cent by amiloride.

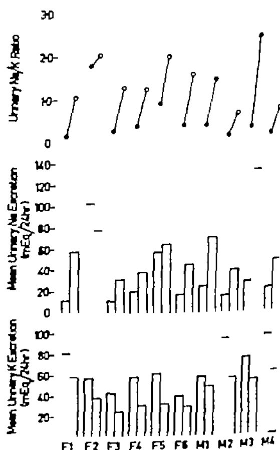


Fig. 1 Comparison of the effect of furosemide and furosemide together with amiloride on the mean sodium and potassium excretion for each patient.

The most significant change on the com bined treatment was the reduction in the potassium excretion in all patients, ac companied by a consistent increase in the sodium/potassium excretion ratios (Fig 1) This effect was retained even when the dose of furosemide used was 120 mg dail in two patients (M1 and M2) The average reduction in potassium excretion during the combined diuretic regime was 35 per cent

Alterations in plasma electrolytes with both drugs were not significant except in one patient (M4) whose serum potassium rose from 5 1 mEq per liter on the first day to 5.8 mEq per liter on the eighth day of the combined drug treatment.

Changes in endogenous creatinine clear ance These are included in Table II Before study all patients had some impairment of endogenous creatinine clearance related to associated cardiac failure there being no evidence of intrinsic renal disease The combination of amiloride and furosemide produced little change except in one patient (F3) who became depleted of sodium and in whom the clearance fell from 58 to 35 ml per minute.

Side effects Amiloride was well tolerated and no subjective effects were reported There was no alteration in the peripheral blood picture produced by the drug and no hepatotoxicity was noted No significant changes in the levels of serum uric acid or fasting blood glucose were observed during the short period of drug adm nistration

Changes in total body potassium The val ues of K_e obtained at the start of each study are given in Table III The mean value for the six women was 1 781 mEq (32 7 mEq per kilogram) and for the four men 2,851 mEq (38 0 mEq per kilogram) Compared with previously reported studies in normal subjects using similar methods [13] both the men ($p < 0\ 001$) and women ($p < 0\ 001$) in the present series showed sig nifcantly reduced levels for exchangeable potassium (expressed as K_e per kilogram) Repeated estimations of K_e at the end of each study showed no significant difference from those at the beginning because the change in total body potassium measured by balance studies over the short du ation of the studies was beyond the sensiti ty of detection by the K_e method

Table III Measurement at the start of the trial of total exchangeable body potassium (^{42}K) in 10 patients previously treated for 3 to 12 months with diuretic drugs

Subject	Mean calculated K (mEq)	K per kilogram of body weight (mEq)
F1	1 859	36 5
F2	1 604	32 7
F3	1 489	39 2
F4	1 759	33 2
F5	2 595	29 5
F6	1 379	25 1
Mean	1 781	32 7
Expected normal mean	449	41 2
M1	2 315	40 6
M2	3 567	39 6
M3	2 750	29 9
M4	2 773	4[illegible] 0
Mean	2 851	38 0
Expected normal mean	3 418	46 8

*From Flear and associates

Discussion

Excessive potassium loss is not uncom mon with the continued use of potent mod ern diuret cs. Recently Remenchik and associates[3] ha e shown that depletion of the body stores of potassium can develop rapidly Of particular importance is the loss of cellular potassium from heart muscle n cardiac fa lure This can occur without the use of digitalis or d uretics[14] which how ever further aggravate the intracellular potassium loss.[15] Sch mert and associates have now confirmed these observations in the human when they measured the so dium potassium ratios in pap llary muscle biopsies obtained during mitral valve re placement. The clinical implications of these findings are apparent Ebert and as sociates[4] described six patients with per sistent hypokalemia following open heart surgery each of whom developed a serious ventricular arrhythmia which responded to potassium repletion All six had been on long term diuretic therapy

An mal and human studies have ind cated that am loride has a moderate natri uretic effect with loss of b carbonate in the

urine and the property of retaining potassium when given alone or in combination with other diuretics.[7,1] This drug has been shown to have a mild but a variable hypotensive effect,[9,21] and pharmacologically its action resembles that of triamterene although amiloride appears to be more potent[1] Its site of action is in the distal renal tubule and it appears to act independently of aldosterone or carbonic anhydrase inhibition

The present study of ten patients extends earlier clinical reports[9,22] and confirms the effectiveness of amiloride as a potassium-sparing agent when given to patients in chronic congestive cardiac failure with significant edema It also potentiates the diuretic action of furosemide. No serious side effects were encountered although mild hyperkalemia developed in one patient in another a significant depression of the endogenous creatinine clearance at tributable to sodium depletion was observed No depression of renal function was found during previous acute investigations and five patients that we have followed for over 12 months have not shown significant renal impairment while taking the drug[22] Seneviratne and Sherlock[9] however have noted fall in creatinine clearance in some patients on amiloride This probably is not a specific effect of the drug and may in many cases be due to an excessive loss of sodium[22]

A striking feature of the results presented in this paper is the potassium depletion in the patients studied Similar results were reported by Lockey and associates[6] in 16 of 23 patients who had been on long term diuretic therapy and who subsequently had open heart surgery All our cases at the time of the initial estimation of exchangeable body potassium were normokalemic and potassium wasting had occurred previously despite oral potassium supplements in 8 cases and despite the administration of spironolactone in 5 cases. All patients had been on diuretic therapy for periods exceeding two months During an 8 day period of combined amiloride-furosemide treatment the mean cumulative potassium retention of approximately 24 mEq per patient per day would suggest that an adequate potassium balance should be achieved during longer periods of combined therapy This has been shown to be possible in 19 of 24 cirrhotic patients given amiloride and ethacrynic acid in combination[9] although the actual figures for exchangeable body potassium which was measured were not reported by Seneviratne and Sherlock in their paper

Hyperkalemia may develop in patients with cirrhosis of the liver or in those with significant renal impairment when amiloride is used alone or rarely when used in combination with a thiazide furosemide, or ethacrynic acid The relative risk of hyperkalemia with amiloride compared with that associated with the use of spironolactone and triamterene has yet to be established The serum electrolytes particularly the serum potassium and the electrocardiogram must be observed regularly in patients treated with amiloride particularly in the first few weeks of treatment or at times of a massive diuresis which are likely to induce sodium depletion It is at these times that most episodes of hyperkalemia have been reported in patients treated with amiloride. As with triamterene and spironolactone[23] its use is not recommended in cases with moderate or advanced renal failure because of the risk of symptomatic hyperkalemia Although treatment with amiloride has been associated with some deaths, these deaths have occurred in patients in whom the underlying disease process itself carried a serious risk to life.

Summary

The effectiveness of the new potassium sparing diuretic amiloride (MK-870) in combination with furosemide has been evaluated by a balance study in 10 patient who had previously been on diuretic therapy for cardiac failure from valvular heart disease The total exchangeable body potassium was measured by 42K dilution principle at the beginning of the study and after an 8 day period of combined amiloride-furosemide therapy From balance data amiloride enhanced the natriuretic response of furosemide by 92 per cent and reduced the potassium excretion by 35 per cent No serious side effects were encountered during the investigation In all patients depletion of total body potassium wa present at the beginning of the study The balance data suggests that pota ium b l

ance should be maintained during long periods of treatment with furosemide together with amiloride The therapeutic implications of the combined diuretic regime in cardiac patients in failure before open-heart surgery are discussed

We wish to thank Dr J B Lowe for permission to study the patients under his care, Mr B White for help with the estimations of exchangeable body potassium, and Mrs E M Smith for secretarial assistance. We are also indebted to Miss Margaret Till and Sister K Gillanders for help with the balance studies. Amiloride was made available by Merck, Sharp and Dohme Research Laboratories.

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Idiopathic mitral subannular left ventricular aneurysm in the Bantu

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Idiopathic aneurysms situated in the submitral, subaortic, or apical regions of the left ventricle occur almost exclusively in the Negroid races, and several reports of this uncommon condition have previously been published by investigators active in Africa.[1-4] At the Cardiac Clinic, Groote Schuur Hospital in Cape Town, we have collected seven cases of the submitral variety, all in Bantu patients, over a period of 5 years (1963 through 1968). It is the purpose of this paper to record the clinical features, diagnostic difficulties, and gratifying results of surgical correction in these patients and to discuss possible etiologic factors.

Description of patients

Age and sex. The ages of the patients varied between 3 and 34 years with a mean of 20 years. There were five females and two males.

Symptoms. Only one patient was asymptomatic; four complained of dyspnea and two had been in frank congestive cardiac failure. Chest pain localized to the third or fourth left intercostal space at the site of the aneurysmal pulsation was present in three patients and one patient presented with a left hemiplegia due to systemic embolization.

Physical signs. At the time of examination there were no signs of congestive heart failure.

The most striking abnormality was an obvious systolic pulsation in the third or fourth left intercostal spaces more laterally situated than the systolic heave usually associated with right ventricular overactivity. This finding was present in five patients; four of these had anterolateral submitral aneurysms where the abnormal pulsation could be directly attributed to the aneurysm. In the fifth subject the aneurysm arose posteriorly, displacing the heart forward toward the chest wall and producing a diffuse heave in this region. In one case with an aneurysm arising from the diaphragmatic surface of the left ventricle, an abnormal pulsation was present in the epigastrium. In only one patient with a small diaphragmatic aneurysm was no abnormal pulsation present.

Murmurs of mitral insufficiency, not always pansystolic, were present in five patients and a soft early diastolic murmur of trivial aortic insufficiency was present in one. In two cases to-and-fro murmurs localized to the site of the abnormal pulsation were present and were attributed to movement of blood in and out of the narrow-necked aneurysm.

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Fig 1 Chest radiograph of patient with anterolateral mitral subannular aneurysm showing large aneurysmal bulge of left upper cardiac border ith displacement of the heart t the right



Fig 3 The chest radiograph of patient with small anterolateral aneurysm showing linear calcification of its wall



Fig 2 The apparently normal chest radiograph of patient with small diaphragmatic aneurysm.

Clinical methods

Chest radiog aphy The radiology of the condition has been well reviewed by Cockshott and associates. In ou series the cardiac outline wa abnormal n six patients. Heart size was increased n three but the aneurysm itself contributed to the large transverse diameter n these Signs of pulmonary congestion were present in three patients.

The most striking abnormal ty was a visible aneurysmal bulge. This was situated at the left upper cardiac border in four cases (Fig 1) where the aneurysm arose from the anterolateral mitral subannular position. In the three patients with posterior aneurysms only one projected to the left and was visible in the posteroanterior projection In another patient the barium-filled esophagus was displaced backward just above the diaphragm in a position somewhat lower than usually seen with left atrial enlargement, and in the third patient no radiologic abnormality was apparent (Fig 2) In two patients the aneurysm was calcified (Fig 3)

The electroc rdiogram The ECG was abnormal in all cases. All showed sinus rhythm and normal P wa es. Four cases showed ST T wave changes only usually n st n dard I V and V_6 Two patient had the pattern of left ventricula hypertrophy and

one had the classical pattern of diaphragmatic infarction (Fig. 4).

Cardiac catheterization. Right atrial pressure was normal in all. Pulmonary artery and right ventricular systolic pressures were moderately elevated (33 to 52 mm. Hg) in four patients, normal in two patients, and not measured in one patient. Left ventricular end-diastolic pressure was normal in three patients (5 to 10 mm. Hg), moderately elevated in one patient (15 mm. Hg) and abnormally elevated in two (25 to 26 mm. Hg). Cardiac indices were all in the normal range (2.5 to 4.7 L. per minute per square meter).

Angiography. Left ventricular angiography was performed in six patients and in one the angiogram followed injection of dye into the pulmonary artery. Aortic angiography was performed in all.

The left ventricular end-diastolic volume was assessed as normal in five and large in

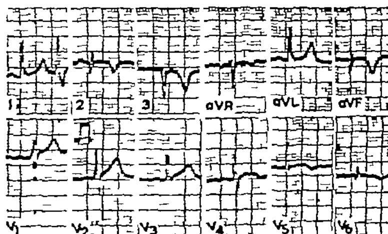


Fig. 4. The ECG of patient with small diaphragmatic aneurysm simulating diaphragmatic myocardial infarction.



Fig. 5. The left ventricular angiogram in the right anterior oblique view of child with a large diaphragmatic ventricular aneurysm. The aneurysm has displaced the left ventricle forward and the left atrium upward. The latter chamber appears compressed and flattened in this view. During ventricular systole radiopaque dye entered both the aneurysm and the left atrium.

two patients, but in only one of these was the degree of emptying assessed as inadequate $\left(\frac{ESV}{EDV} > 50 \text{ per cent}\right)$.

Mitral insufficiency was present in all patients studied by left ventricular angiography.

All patients had the characteristic features of a mitral subannular aneurysm. The orifice was small and situated immediately beneath the mitral annulus. Four aneurysms arose anterolaterally and three from the diaphragmatic or posterior aspect of the left ventricle (Fig. 5). In five patients the aneurysm was large and equal in size to the left ventricular cavity and in the remaining two patients about one half the size of the left ventricle (Fig. 6). All aneurysms showed abnormal systolic pulsation. At least one was multilocular (Fig. 7) and two showed obvious soft tissue shadows,



Fig. 6. The left ventricular angiogram in the posteroanterior projection in the patient whose chest radiograph is shown in Fig. 3. The injection was made directly into the aneurysm.

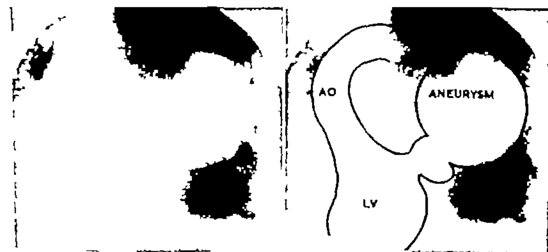


Fig. 7. The left ventricular aneurysm of a patient with a small anterolateral aneurysm which has ruptured and formed a large false aneurysm giving it a bilocular appearance.

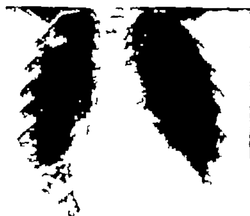


Fig. 8. The chest radiograph of the patient whose preoperative film is shown in Fig. 1 three years after successful surgical repair.



Fig. 9. The chest radiograph of a patient with a sinus of Valsalva aneurysm which burrowed into the left ventricular myocardium and ruptured into the cavity of the left ventricle, in whom an incorrect clinical diagnosis of idiopathic left ventricular aneurysm was made, largely on the radiological appearances. The correct diagnosis was established by aortic angiography and confirmed at surgery.

beyond the contrast filled cavity suggesting extensive mural thrombosis.

Aortic angiography showed a competent aortic valve in all. In one case a small unruptured sinus of Valsalva aneurysm arising from the right coronary sinus was also present.

Course and treatment

Six patients were subjected to surgery under cardiopulmonary bypass. In the seventh patient the operation has been delayed to assess the degree of recovery from the hemiplegia. At surgery the aneurysms were found to be fibrous-walled, often with extensive mural thrombosis and calcification. In two cases rupture had occurred with the formation of false aneurysms giving a multilocular appearance. The orifice situated immediately below the atrioventricular groove was a narrow slit-like opening about 1 cm. in length and could sometimes be closed by direct suture but usually required to be oversewn with an Ivalon patch.

All patients survived the operation with an uneventful postoperative course. Heart size returned to normal and mitral murmurs disappeared in all but one. Three patients followed for a period of at least three years after the operation have remained asymptomatic with normal hearts clinically and radiographically (Fig. 8) but the ECG has remained abnormal.

Histology. The wall of the resected aneurysm was composed of dense collagenous fibrous tissue in all cases and in only one case were a few muscle fibers visible near its origin.

Discussion

The diagnosis of this condition presents few difficulties in cases with anterolateral aneurysms. The combination of an aneurysmal pulsation in the third intercostal space with a mitral systolic murmur, a chest radiograph showing an obvious aneurysmal bulge anterolaterally, and an abnormal ECG in a young Bantu patient is quite typical. Difficulties do arise when the aneurysm arises posteriorly and does not produce abnormal systolic pulsation or an obvious aneurysmal bulge in the posteroanterior chest radiograph. A clinical diagnosis of mitral insufficiency was made in the two patients 3 and 5 years of age with posterior aneurysms. The correct diagnosis was made by left ventricular angiography undertaken to determine the cause of mitral incompetence apparently not due to rheumatism. In the third case with posterior aneurysm the diagnosis was suspected because of the electrocardiographic pattern of diaphragmatic infarction which as Chesler and associates[4] have pointed out should lead one to suspect idiopathic left ventricular aneurysm as myocardial infarc-

tion is excessively rare in this racial group. Other disorders may closely mimic idiopathic left ventricular aneurysm Such a disorder is, in particular a sinus of Valsalva aneurysm which has burrowed into the left ventricular myocardium and ruptured into the cavity of the left ventricle (Fig 9) The clinical signs of a large aortic run-off and the aortic angiogram showing the aortic sinus aneurysm are the differentiating points.

The occurrence of heart failure is probably due to a combination of several factors all of which appear to be reversible by excision of the aneurysm In some cases the large size and elasticity of the aneurysms lead to an increase in systolic compliance and may cause defective development of tension during the isometric period The relatively small orifice to some extent counteracts this effect and also accounts for the rarity of systemic embolization.[7] The distortion of the mitral valve apparatus with resultant mitral incompetence produces a similar hemodynamic burden on the left ventricle and may in addition cause elevation of left atrial pressure Finally distortion of the coronary arteries by the aneurysms with resultant myocardial ischemia has been mentioned[3] as a possible factor though the ECG changes including the infarct pattern could just as easily be produced by the local effects of the aneurysm rather than by coronary artery obstruction

The etiology of this condition is obscure. We would agree with Abrahams and coworkers[2] and Chesler and associates[7] that a congenital defect is likely because of the young age at which it occurs, the stereotyped site of origin in the mitral subannular position and the complete normality of the rest of the myocardium The association of a sinus of Valsalva aneurysm in one of our cases suggests that the defect may involve the attachments of the left ventricular myocardium or aorta to the fibrous mitral and aortic annuli. The almost exclusive occurrence in the Negroid races remains unexplained

Previous reports have stressed the difficulties of surgical correction but these appear to have been overemphasized The results of surgical correction are in fact highly gratifying as the lesion is completely and permanently cured most cases losing all their symptoms and abnormal physical signs including the mitral systolic murmurs The ECG s, however not unexpectedly remain abnormal after surgery

Summary

Seven cases of idiopathic mitral subannular left ventricular aneurysm in Bantu patients are reported. The symptoms, physical signs, electrocardiographic and radiologic changes, together with the findings at catheterization angiography and surgery are presented The problems in diagnosis, hemodynamic abnormalities, etiology and surgical treatment are briefly discussed

We wish to thank our surgical colleagues for the confirmation of the diagnosis in six of our seven patients and Dr J G. Burger the Medical Superintendent, for permission to publish.

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Familial occurrence of Wolff Parkinson White syndrome

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In recent years an increasing number of disease entities has proven to be due to heritable genetic or chromosomal abnormalities. Identifying familial disorders is of obvious value now in counseling affected individuals contemplating parenthood fur thermore the future possibility of correcting faulty genetic material exists.

The purpose of this paper is to report a familial occurrence of Wolff Parkinson White syndrome in which current chromosome inspection and counting techniques have been utilized

Case histories

The first member of the K. family t be examined was Mrs. B K. age 45, *h presented nth history* of hypertension of tv year duration She unaware of having the Wolff Parkinson-White syn-drome She gave a vague history of palpitations and n occasional pid heart rate for ma y years Aside from a moderate degree of hypertension minimal retinal changes, hyperostosis frontal interna on the skull x-ray nd Wolff Parkinson-Wh t pattern on the electrocardiogram (Fig 1), her history physical examination, nd laboratory data ere normal Her son S. K. ge 15 had 6 year history of rapid heart rate, hich occurred 1 t 6 times a year lasted 5 to 60 minutes and topped spontaneously or th deep respiration Physical examination and extensive laboratory data were nremarkable except for previously undiagnosed Wolff Parkinson-Whit pat tern on the electrocardiogram (Fig 2). Her husband F K., age 49 and other son, J K., age 18 revealed no abnormality on history physical, nd laboratory data, including the electrocardiogram. Vectorcardiograms performed on S. K. and B. K. were compatible th the elect card gr phic diagnosis of Wolff P rkinson Whit yndrome V ect rcardiogram on J K. wa normal Chromosome anal ses on B K. J K. nd S. K. ere normal

Information ls sought concerning the parent three brothers, nd one sister of B K., 8 more distant relatives There as no know history of Wolff Parkinson Wh te ndrome in other f mil members. Existing lectrocardiograms on the mother nd four siblings of B K. ere examined and ere neg t ve for Wolff Parkinson-White syndrome I terestingly t brother of B. K. ere said t have had Leber disease hereditary often sex linked, form of optic neuritis but this could not be documented.

Discussion

Six previous instances[1] of familial occurrence of isolated Wolff Parkinson White syndrome were noted in the medical literature (Table I) since Wolff Parkinson and White initially described the disorder in 1930.[7] The incidence of Wolff Parkinson-White syndrome was approximated by Averill and associates[8] in 1960 They found 109 cases out of 167,375 electrocardiograms examined Katz and Pick found 81 cases in 50 000 consecutive electrocardiograms in 1956 A sex preponderance exists 54 to 70 per cent are males [1,10,11] The probability of chance occurrence in related individuals is obviously small. Tending also to support a congenital etiology are a number of cases documented in infants including the newborn [11-]

A higher incidence has been noted in

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Kindly performed by Dr Jean Smith at he Veterans Administration Hospital, Bronx, N Y

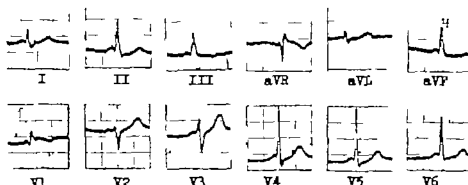


Fig. 1

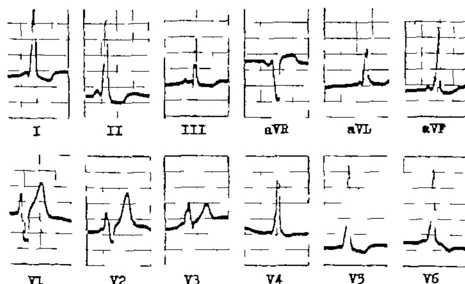


Fig. 2

Table I. Previously reported cases of isolated familial Wolff-Parkinson-White syndrome

Author	*Year*	*Familial occurrence of Wolff-Parkinson-White syndrome*
Öhnell	1944	Family 1 4 of 6 siblings Family 2 2 of 10 siblings
Dommer	1951	Mother and adult son
Willis	1953	Father and 3 of 6 children
McIntire	1955	Mother, age 28, and son, age 8 months
Averill	1956	Brothers, ages 50 and 57
Harnischfeger	1959	Three generations in one family. Grandfather, father, identical girl twins, and male of fraternal twins

patients with certain gross congenital heart defects. Donzelot found three instances of Wolff-Parkinson-White syndrome in 1,100 patients with congenital heart disease and Hecht found three cases in 350 such patients. A particularly significant correlation seems to exist between Wolff-Parkinson-White syndrome and Ebstein's anomaly of the tricuspid valve,[2, 22, 23] familial cardiomegaly,[23, 24] and dextrocardia. Schiebler and associates[23] also described an instance of Wolff-Parkinson-White syndrome occurring in a child with mental retardation, optic atrophy, seizures, and hyperactive deep tendon reflexes and commented on a possible relationship between Friedreich's ataxia and familial cardiomegaly.[23] He noted an incidence of Wolff-Parkinson-White syndrome in one of 200 children with congenital heart disease.

Conclusions and summary

A familial occurrence of Wolff-Parkinson-White syndrome in mother and son has been described. Chromosome analysis failed to reveal any abnormality. The probability, however, of finding a gross chromosomal disruption was small, since a defect causing isolated Wolff-Parkinson-White syndrome would be more likely to have occurred at the gene level. In addition, there may be multiple etiologies, including nonheritable ones, at cause.

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Perfusion and ventilation radioisotope lung scans in stenosis of the pulmonary arteries and their branches

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Stenosis of the pulmonary arteries and their branches can be suspected clinically by the finding of a precordial murmur that is of equal or greater intensity at the back and axilla. The diagnosis is confirmed by right heart catheterization and angiography.[1-4]

If the stenosis is unilateral or greater on one side, then less blood flow would be anticipated on the most severely affected side. The present study was undertaken to determine whether a correlation exists between the relative distribution of right and left pulmonary blood flow with the degree of stenosis.

To evaluate relative pulmonary blood flow, the distribution of radioactivity on the scintillation lung scan after injection of ^{131}I macroaggregated albumin (MAA) was utilized since a correlation between pulmonary arterial blood flow and distribution of radioactivity has been previously established.[5-12] Scintillation scanning of the lungs after inhalation of xenon 133 gas was performed to evaluate whether a chronic decrease in pulmonary perfusion would affect the relative right to left distribution of ventilation.[13]

Selection of patients

The subjects of this study were chosen from a group of 22 patients seen in the cardiac clinic of the Handicapped Children's Division of the District of Columbia General Hospital. All had documented stenosis of the pulmonary arteries and its branches and were reported by Rios and associates. Nine of these 22 patients were selected on the basis that they had cardiac catheterization including angiography and that they did not have a history of lung disease. They were between 5 and 20 years of age. Of these nine patients, six had no other cardiac lesion, two had pulmonary valvular stenosis, and one had pulmonary infundibular stenosis and partial anomalous venous return. Subsequent to this selection, another patient with pulmonary

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branch stenosis was studied and was included in this series. All of the patients in this study had coarctation of the right, left or both pulmonary arteries. This would be classified as Type I according to Franch and Gay.[14]

Methods

The diagnosis of stenosis of the pulmonary arteries was substantiated by angiography and by the measurement of the systolic gradient in the pulmonary arteries during right heart catheterization. Pulmonary angiograms were done by injecting contrast material into the pulmonary artery or right ventricle using a pressure injector. Dye curves were obtained using cardiogreen dye and a Gilford densitometer.

The radioxenon ventilation lung scans were done first with the subject in a sitting position. After a noseclip and a mouthpiece were applied, the subject was allowed to breathe room air for 20 to 30 seconds while background counts were recorded. At the end of a normal expiration a full breath of air/xenon 133 mixture was inhaled and respiration held while the initial posterior scan was taken. Fifteen second rebreathing scans were taken for one minute. After the patient stopped inhaling xenon 133, further scans were taken at 15 second intervals until xenon 133 was eliminated from the lungs. The equipment and arrangement used are the same as described by Surprenant and associates.

After a 20 to 30 minute delay the patients were then given 300 microcuries of MAA intravenously after lying supine for several minutes breathing quietly. In most cases there was no difficulty in viewing the entire chest in the camera field. In a few instances where this could not be done because of chest size, individual projections of the right and left sides were taken and composites made. Since the radioxenon was excreted rapidly, there was no interference with the later MAA studies.

Results

The distribution of activity in the perfusion lung scan and the degree of stenosis are depicted in Table I.

Three patients (B. M., M. S. and D. F.) had unilateral stenosis of the pulmonary artery. The most marked degree of stenosis was present in Patient B. M. who was previously reported on by Masoumi and coworkers.[17] This subject had documented stenosis of the right pulmonary artery without a murmur. Acoustically silent pulmonary stenosis occurred because the stenosis was so severe that there was little or

Table I. Pulmonary artery pressure, perfusion and ventilation lung scans in 10 patients with stenosis of the pulmonary arteries

Patient	Pressure (mm. Hg) RV	MPA	RPA	LPA	Degree of stenosis*	Perfusion (%) RL	LL	Ventilation (%) RL	LL
B. M.	36/3	33/10	10/7	31/8	R >> L	12	88	45	55
M. S.	28/5	26/3	14/3	23/5	R >> L	35	65	57	43
D. F.	27/6	21/9	12/7	20/6	R >> L	44	56	55	45
C. B.	58/8	50/2	7/3	17/3	R > L	50	50	55	43
R. G.	98/6	41/18	35/16	18/5	L > R	65	35	59	41
J. N. F.	55/2	50/15	20/10	30/12	R > L	27	63	58	42
K. Y.	37/3	35/10	20/10	15/6	L ≥ R	61	39	55	45
S. C.	30/7	30/2	29/13	22/10	L ≥ R	57	43	49	51
W. J.	42/8	32/13	26/7	32/13	R ≥ L	59	41	54	46
W. C.	38/6	35/8		18/9	—	56	44	55	45

Abbreviations: RV, Right ventricle; MPA, main pulmonary artery; RPA, right pulmonary artery; LPA, left pulmonary artery; RL, right lung; LL, left lung.

*Degree of stenosis is the relative degree of coarctation of the right and left pulmonary arteries by systolic pressures recorded in these vessels: >>, unilateral stenosis; >, systolic pressure difference greater than 10 mm. Hg; ≥, systolic pressure difference less than 10 mm. Hg.

**Right pulmonary artery could not be entered.

no blood flow across the stenotic segment. In our studies on this patient, the perfusion lung scan showed that 12 per cent of the radioactivity was distributed to the right lung and 88 per cent to the left lung reflecting a severe decrease in blood flow. For comparison, a normal distribution is 52 ± 3 per cent to the right lung and 48 ± 3 per cent to the left lung.[4,16] This marked shift in blood flow was associated with only a slight shift in the ventilation scan (Fig. 1). Normal values for ventilation lung scans obtained from a group of 20 normal volunteers are 52 ± 2 per cent to the right and 48 ± 2 per cent to the left lung.[19] These values are in agreement with other experience.[21] The findings in the present study are consistent with previous reports that chronic abnormalities in perfusion cause only slight changes in the distribution of ventilation.[22,23]

Three subjects (C. B., R. G., and J. N. F.) had bilateral stenosis of the pulmonary arteries on angiography with 10 mm. Hg or greater difference in the systolic pressures between the left and right pulmonary arteries. Under these circumstances there was good correlation between the difference in blood flow distribution to the right and left lungs by MAA scan and the degree of stenosis of the pulmonary artery. Case J. N. F. (Fig. 2) is an example of this type



Fig. 1. Pulmonary angiogram, together with pulmonary arterial pressure in mm. Hg (above) and 131I MAA perfusion and 133xenon ventilation scans in Patient B. M. with severe unilateral stenosis of the right pulmonary artery. Note that in this, and in subsequent figures, the scans were taken in the posterior position with the left lung shown on the *left* side of the figure. In contrast, the angiogram was taken in the anterior position with the left pulmonary artery visualized on the *right* side of the figure. *RPA*, Right pulmonary artery; *LPA*, left pulmonary artery; *MPA*, main pulmonary artery.

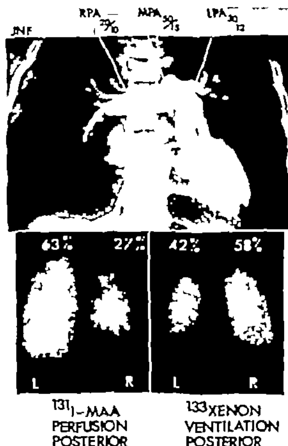


Fig. 2. Right ventricular and pulmonary artery angiogram (above) and lung scan (below) in Patient J. N. F. with bilateral coarctation of the pulmonary arteries. The stenosis appears to be more severe in the left than in the right pulmonary artery, and the distribution of blood flow reflects this difference in stenosis. (Labelling and abbreviations as in Fig. 1.)

of lesion. There was a systolic pressure of 20 mm. Hg in the right pulmonary artery and 30 mm. Hg in the left pulmonary artery. The perfusion lung scan showed a distribution of 37 per cent of the radioactivity to the right lung and 63 per cent to the left lung. This demonstrates a good correlation between the alteration of blood flow with the degree of stenosis.

Three subjects had bilateral coarctation of the pulmonary arteries with less than 10 mm. Hg difference between the systolic pressures in the left and right pulmonary arteries. The distribution in blood flow correlated well with the pulmonary artery pressure in two of the three patients. Patient W. J. showed an unexplained shift of blood flow toward the side with the greatest degree of stenosis as measured at catheterization. The ventilation scans are relatively normal in these three subjects.

Four patients showed areas of patchy decrease in radioactivity in the lungs in both the perfusion and ventilation lung scans. The decrease in ventilation as well as perfusion to localized areas was thought to be inconsistent with stenosis of the pulmonary arteries.

Discussion

The relative right and left pulmonary arterial blood flow determined by the perfusion lung scan showed a good correlation with the catheterization pressure gradients and the angiographic findings. In the setting of a patient with a systolic precordial murmur that is of equal intensity or louder in the back and axilla, the maintenance of relatively normal ventilation in the presence of altered perfusion is in accord with the diagnosis of stenosis of the pulmonary arteries. The results of this study suggest that a systolic pressure gradient of 10 mm. Hg or greater between right and left pulmonary arteries predictably alters perfusion. Ventilation remains relatively unaffected. A pressure difference of less than 10 mm. Hg appears to be insufficient to cause consistent alterations in the distribution of blood flow. Therefore, it is possible to have bilateral stenosis of the pulmonary arteries without changing right and left distribution of either pulmonary blood perfusion or ventilation. In these cases normal perfusion and ventilation scans cannot be used as evidence to exclude this diagnosis.

Alteration of blood flow distribution with normal ventilation studies may also be seen in patients with pulmonary emboli.[9,10] However, this condition is not likely to cause confusion in the asymptomatic younger age group without gross evidence of heart disease. Pulmonary artery atresia will have a markedly altered perfusion with relatively normal preservation of ventilation.[11] These patients do not have the murmurs described in patients with stenosis of the pulmonary arteries. However, the differential diagnosis between pulmonary artery atresia and coarctation of the pulmonary arteries may be impossible clinically. This problem was exemplified in Patient B. M., in whom the differential diagnosis was elucidated only by means of angiography.

As yet there are insufficient published data to exclude other types of congenital heart disease that may have patterns of perfusion and ventilation similar to those described here in patients with stenosis of the pulmonary arteries. However, we could find no reports of alteration in right to left blood flow distribution in acyanotic congenital heart disease. Pulmonary hypertension with intracardiac shunts or pulmonary hypertension due to mitral stenosis results in a shift of blood flow to the upper lobes, but there does not appear to be a right- or left-sided shift in blood flow.[12,13] It has been shown that ventilation and perfusion to the lung remain normal in patients with atrial septal defect.[14] Since patients with atrial septal defect may also have murmurs that simulate those of stenosis of the pulmonary arteries,[15] the ventilation perfusion lung scans may help distinguish this murmur apparently due to excessive flow in the pulmonary arteries from an anatomic stenosis.

The perfusion scan and the ventilation scan, when done correlatively, may be utilized to provide information not available by cardiac catheterization. For example, in Subject W. C. (Fig. 3), the right pulmonary artery could not be entered during catheterization. Pulmonary angiography demonstrated bilateral coarctation of the pulmonary arteries. The distribution of blood flow was nearly equal by perfusion lung scan.

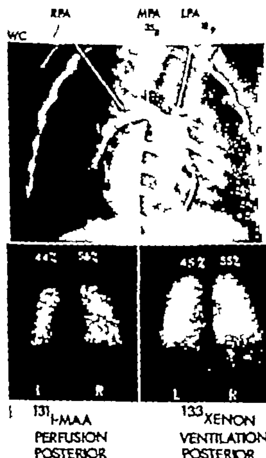


Fig. 3. Pulmonary angiogram (above) in Patient W. C. in whom the catheter could not be advanced into the right pulmonary artery. The MAA scans (below) suggest that there is obstruction of the right pulmonary artery to a degree nearly equal to that in the left. (Labeling and abbreviations as in Fig. 1.)

On the basis of the good correlation between pulmonary blood flow distribution and degree of stenosis found in other patients in this study, it may be assumed that the degree of stenosis of the right and left pulmonary arteries were relatively equal. Thus, the perfusion lung scan may be valuable in the diagnosis of stenosis of both pulmonary arteries when one pulmonary artery pressure is unobtainable.

Finally, if suspicion of stenosis of the pulmonary arteries is aroused clinically, the perfusion lung scan is such a safe and simple test that it should be done prior to cardiac catheterization in order to properly plan to document this condition by appropriate measurements and procedures.

In the present study several patients were found to have previously unsuspected lung disease as shown by the lung scans. These results may represent congenital anomalies of the bronchial vascular structures in the lungs. It is suggested that perfusion and ventilation scans be done routinely in patients with stenosis of the pulmonary arteries in conjunction with other appropriate spirometric studies in order to determine the true incidence of emphysema or other presently unidentified lung disease in these patients.

Summary

In ten patients with stenosis of the pulmonary arteries, the relative distribution of right and left pulmonary blood flow was related to the localization of the coarctation by angiography and the degree of stenosis. To evaluate the distribution of pulmonary blood flow, the scintillation lung scan after injection of ^{131}I macroaggregated albumin (MAA) was utilized. Scintillation scanning of the lungs after inhalation of xenon 133 gas was also performed to assess the distribution of ventilation.

The relative right to left pulmonary arterial blood flow distribution showed a good correlation with the catheterization pressure gradients and the angiographic findings. The distribution of ventilation was relatively unaffected. In a patient with a precordial murmur that exhibits disproportionate radiation to the axilla and back, an altered distribution of right to left perfusion helps to substantiate the diagnosis of stenosis of the pulmonary arteries. However, if the obstruction is bilateral and of equal degree, the distribution of blood flow may be normal. In patients with isolated acyanotic left to right shunts, the right to left distribution of pulmonary blood flow is apparently unaltered so that a lateral shift from the normal pattern raises the question of stenosis of the pulmonary arteries as an additional lesion. The finding of patchy areas of decreased radioactivity in both perfusion and ventilation lung scans in four of ten patients suggest that there may be a high incidence of emphysema or other lung disease in these patients.

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Gordon Ew y J seph I erloff and Robert O'Rou k
f r criti l review f the man script nd t M
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Experimental and laboratory reports

Estimation of left atrial size using ultrasound

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The size of the left atrium can be an important clue in the differential diagnosis of several forms of acquired or congenital heart disease. Conventional chest roentgenograms and cardiac fluoroscopy are helpful in estimating the size of this chamber. However, the accuracy of these procedures is limited and at times the findings can be misleading. Since the anterior wall of the left atrium, the atrioventricular wall, and usually at least one or both of the lateral walls are within the roentgenographic cardiac silhouette, it is rarely possible to obtain a true left atrial dimension with plain chest roentgenograms. Thus the posterior press on the esophagus, a common radiographic sign of an enlarged left atrium, sometimes can be due to an enlarged right or left ventricle.[4] Even the radiographic prominence of the left atrial appendage is not always proportional to the size of the atrium.

Because of the inadequacy of conventional roentgenograms, angiocardiographic methods have been developed for quantitating left atrial volume.[1-6] These procedures, however, possess a distinct hazard for the patient and are not suitable for routine or repeated cardiac examinations. The present study describes a simple and safe technique for estimating the size of the left atrium by means of diagnostic ultrasound.

The principles of pulsed reflected ultrasound have been described in previous papers.[7-10] Diagnostic ultrasound has the capability of recording or visualizing structures within the roentgenographic cardiac silhouette. This capability has permitted the development of ultrasonic techniques for detecting and assessing the severity of mitral stenosis and pericardial effusion.[7] Newer developments include ultrasonic methods for measuring left ventricular stroke volume[11] and left ventricular wall thickness.[12] All of these examinations have the advantage of being bedside procedures which can be done in a matter of minutes with absolutely no discomfort or risk to the patient.

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Methods

Ultrasound examinations were obtained on 21 normal subjects and 47 patients with various forms of heart disease shortly before diagnostic cardiac catheterization. Twenty-eight of these patients had selective left atrial cineangiocardiography with injections either in the left atrium or pulmonary artery. The cineangiocardiograms were recorded on 35 mm film and were obtained with the patient in the right anterior oblique position. The area of the left atrium as visualized on the cineangiocardiogram was measured using a planimeter. The cine frame corresponding to ventricular end-systole was used for the determinations. The areas were corrected for x-ray distortion by comparing the area of the radiographic image of a piece of lead to its known size.

Plain chest roentgenograms and cardiac fluoroscopy were obtained on the patients undergoing cardiac catheterization. The roentgenograms were interpreted by a cardiac radiologist as to the size of the left atrium according to the following criteria (Table I). The normal sized left atrium (0) was diagnosed when the atrial appendage was not visualized on the frontal view and there was no press on the barium-filled esophagus. Slight left atrial enlargement (I) was indicated by the visualization of the left atrial appendage on the frontal view. When there was easily identified displacement of the barium filled esophagus but the body of the left atrium was not border forming on the frontal projection, the left atrium was considered to be moderately enlarged (II). A left atrium was labeled as large (III) when its body was border forming in the frontal view. Grade IV was reserved for giant left atria. None of the patients in this study were thought to be in this category.

The ultrasound examinations were done with a commercially available ultrasonoscope utilizing a 0.75 inch diameter 2.25 megahertz transducer with a repetition rate of 1,000 impulses per second. The examinations were done with the patient in the recumbent position. The transducer was placed along the left sternal border in the third intercostal space or in rare cases in the second or fourth intercostal space in those patients with unusually high or low diaphragms. A sonic gel was used to ensure

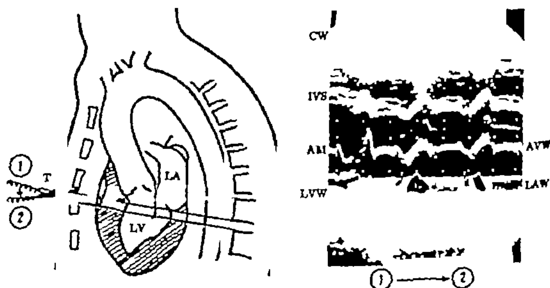


Fig. 1. Method for recording interventricular septum (IVS), left ventricular wall (LVW) and left atrial wall (LAW) echoes. With the transducer (T) in the third intercostal space (position 1), the probe is directed so as to record the echo from the anterior leaflet of the mitral valve (AM). The transducer is then tilted superiorly (position 2), and the contour of the AM echo changes into the AVW echo. The left ventricular wall (LVW) echo also changes into the LAW echo. An electrocardiogram is recorded between the AVW and LAW echoes. LA, Left atrium; LV, left ventricle; CW, chest wall.

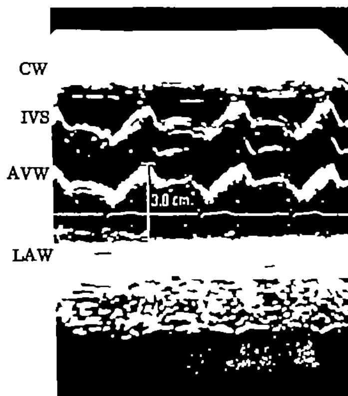


Fig. 2. Measurement of left atrial dimension (*LAD*) in normal subject. Calibration dots are 1 cm. apart vertically. Symbols as in Fig. 1

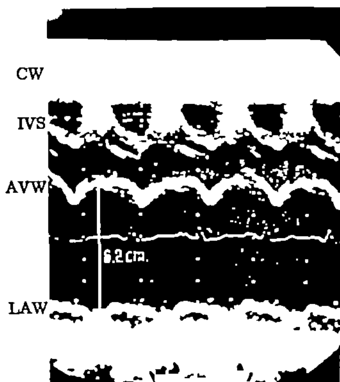


Fig. 3. Left atrial dimension in patient with large left atrium. Symbol as in Fig. 1

airless contact between the transducer and the skin. The probe was pointed initially posteriorly and usually a little medially in order to visualize the anterior leaflet of the mitral valve which was recognized by a well-described characteristic pattern of motion[1-4] (Fig. 1 position 1). A simultaneous electrocardiogram helped with the identification of the cardiac echoes. Gradually the transducer was pointed superiorly and a little more medially (Fig. 1 position 2). The anterior mitral valve echo then lost its characteristic pattern. The amplitude was reduced from about 2 cm. to 1 cm. and the echo lost its rapid motion with early diastole. The pattern of motion was similar to that described previously for the mitral annulus[1] or the atrioventricular wall.[7] With the transducer in this position the sensitivity control which regulates the near field ("near gain") was adjusted to bring out another almost identical echo which was about 2 to 4 cm. anterior to the atrioventricular echo (Fig. 1). This echo was thought to originate from the interventricular septum (IVS). In addition, another echo was recorded posterior to the atrioventricular wall echo. This echo usually exhibited relatively little motion. When it did move it moved posteriorly with ventricular systole. The origin of this echo was thought to be from the posterior wall of the left atrium (LAW) (Figs. 1 and 2). Behind this echo was a large group of echoes stemming from either the lung or mediastinum.

A left atrial dimension (LAD) was obtained by measuring the distance between the atrioventricular wall echo (AVW) and the posterior left atrial wall echo (LAW) at the end of ventricular systole (Fig. 2). The measurement was facilitated by calibration dots which were 1 cm. apart.

Table I. Estimation of left atrial size using ultrasound, chest roentgenograms, and angiography

Patient No.	Age	Sex	Diagnosis	Ultrasound LAD (cm.)	Chest roentgenogram (0-III)	Angiogram LA area (cm.)
1	46	F	MS	5.3	II	55.5
2	41	M	AS, AI	5.0	II	56.1
3	40	F	AI, MS	5.3	II	54.6
4	36	F	MS	4.4	II	42.1
5	60	F	MS, MI	5.1	III	59.1
6	41	M	MS	5.5	II	59.7
7	56	M	AS, AI, MS, MI	5.2	III	61.4
8	30	F	AI, MS, MI	5.0	I	56.8
9	27	F	MS	4.0	II	44.1
10	37	F	MS	4.4	0	46.2
11	60	M	AI, MI, TI	6.4	III	61.8
12	51	F	AS	4.3	I	46.8
13	23	F	AI, MI	6.2	III	69.9
14	23	F	Normal	2.5	0	33.9
15	38	F	MS	4.3	II	50.7
16	54	F	MS	6.5	III	63.5
17	30	F	AS, AI, MS, MI	4.1	II	38.9
18	28	F	AI, MS	4.1	II	42.4
19	55	F	MS	4.8	II	45.4
20	71	F	Heart failure	4.8	II	48.7
21	50	F	AI, MS, MI	4.0	II	33.9
22	41	M	MS	4.3	II	37.6
23	49	M	AI, MS, MI, TI	5.8	II	59.2
24	49	F	MS, MI, TI	4.4	II	39.3
25	30	M	MS, MI	4.2	II	39.5
26	40	F	MS, MI, AI	3.1	0	30.5
27	43	F	MS, MI	5.5	II	65.3
28	43	M	AI	2.8	0	26.2

Abbreviations: LAD, left atrial dimension; LA, left atrium; MS, mitral stenosis; AS, aortic stenosis; AI, aortic insufficiency; MI, mitral insufficiency; TI, tricuspid insufficiency.

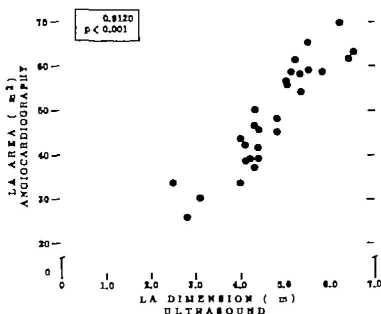


Fig 4 Correlation between the ultrasound left trial dimension and left trial area as determined on the cineangiocardiograms.

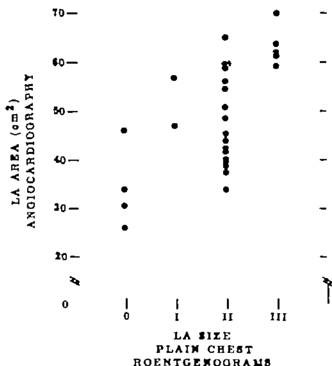


Fig 5 Comparison of radiologist estimate of left atrial size from plain chest roentgenograms with left atrial area as determined on th cineangiocardiograms.

Results

Fig. 2 shows the ultrasound left atrial dimension (LAD) in a normal subject. The measurement was 3.0 cm. Fig. 3 illustrates the findings in a patient with a large left atrium. In this case the LAD measured 6.2 cm. The results of the 28 patients who had left atrial cineangiocardiograms, ultrasound measurements, and routine cardiac fluoroscopy are shown in Table I. Most of the patients had valvular heart disease. The statistical correlation between the ultrasound left atrial dimension (LAD) and the left atrial area on the cineangiocardiograms was excellent (r = 0.9170, p < 0.001) (Fig. 4). On the other hand, there was a great deal of scatter and overlap when comparing the angiocardiograms and the radiologist's estimate of left atrial size from the chest roentgenogram (Fig. 5). The radiologist both overestimated and underestimated the left atrial volume.

Among the normal subjects the mean LAD was 3.1 ± 0.5 cm with a range of 1.8 to 4.0 cm. This measurement correlated with the body surface area (r = 0.6944, p < 0.001) (Fig. 6). Dividing the LAD by the BSA reduced the normal range (1.2 to 2.0 cm. per square meter). Fig. 7 provides the LAD/BSA measurements on the 21 normal subjects and on all 47 patients studied with cardiac catheterization and ultrasound. The patients were divided into those with mitral valve disease, aortic valve disease, bivalvular disease, and atrial septal defects. All but 1 of the 31 patients with mitral or bivalvular disease were outside the normal range. The measurements in 8 of the 11 patients with aortic valve disease were abnormally high. The patients with atrial septal defects were at the upper limits of normal. The graph indicates that the *normal* range of LAD/BSA was 1.0 to 2.0 cm. per M²; mild left atrial enlargement was approximately 2.0 to 3.0 cm. per M²; moderate enlargement was 3.0 to 4.0 cm. per M²; and marked enlargement was over 4.0 cm. per M².

Discussion

There have been earlier attempts to measure the size of the left atrium with ultrasound. Edler[17] demonstrated this in cadavers with the transducer in the third intercostal space and directed posteriorly toward the anterior mitral valve; the ultrasound beam passes through the right ventricle, the interventricular septum, the left

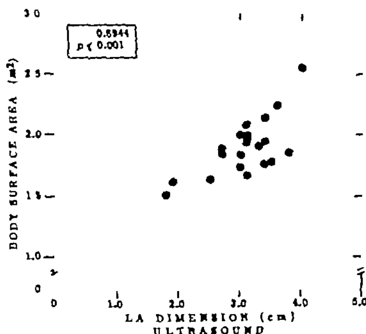


Fig. 6. Correlation between the ultrasound left atrial dimension and body surface area among the normal subjects.

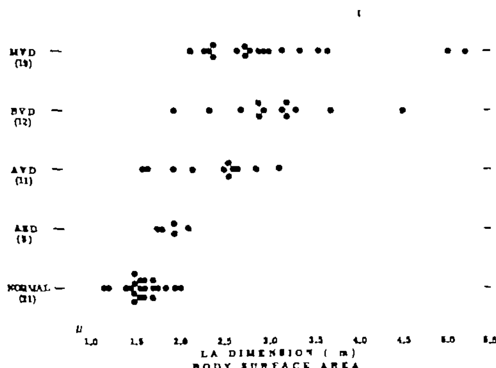


Fig 7 Left atrial dimension divided by body surface area in all 68 patients studied *MVD* Mitral valve disease *BVD* bivalvular disease *AVD* aortic valve disease *ASD* atrial septal defect.

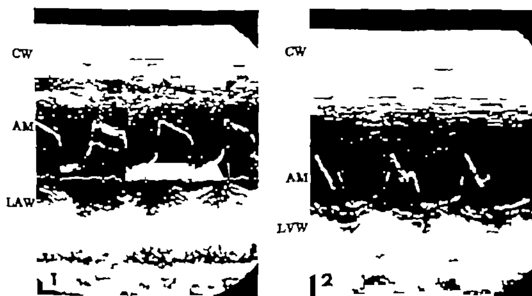


Fig 8 Mitral valve echo (*AM*) in patient with mitral stenosis (recording *1*) and in patient with aortic insufficiency (recording *2*). In recording *1* the left atrial wall (*LAW*) is recorded whereas the left ventricular wall (*LVW*) echo is seen in recording *2*. *LAW* and *LVW* can be differentiated by their opposite motions during ventricular systole.

ventricular cavity the anterior leaflet of the mitral valve the left atrial cavity and then through the posterior wall of the left atrium. Thus it was suggested by some investigators that an estimate of left atrial size could be obtained by measuring the distance between the mitral valve echo and the posterior echo of the left atrium. There are problems with this technique however. First of all this method sometimes fails in cases with enlarged left ventricles and severely rotated hearts. Fig. 8 shows the results of such an examination on two different patients. The left photograph (recording 1) is of a patient with mitral stenosis. As expected the left atrium lies behind the mitral valve echo. The recording on the right (recording 2) is from a patient with aortic insufficiency. Now the left ventricle as identified by its anterior motion with ventricular systole and not the left atrium is recorded posterior to the mitral valve, and a measure of left atrial size is not possible. Another problem is that it is possible to record the mitral valve echo from either the third or fourth intercostal space on the same patient. When the transducer is in the fourth interspace and pointed superiorly the left atrium usually lies behind the mitral valve (Fig. 9 photograph 3). When recording the mitral valve from the third interspace the transducer is directed more inferiorly and the left ventricle is frequently recorded (Fig. 9 recording 1).

The technique used in this study avoids these problems by limiting the examination to the third interspace and by using the atrioventricular ring rather than the mitral

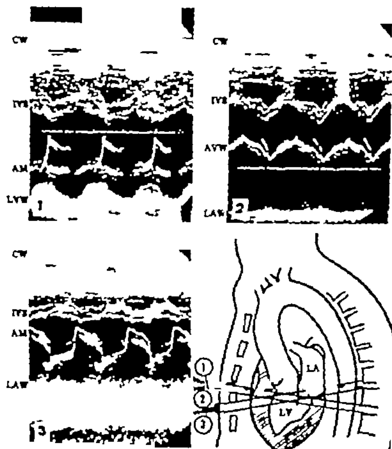


Fig. 9. Diagram and three different ultrasound recordings on the same patient. Recording from position 1 in the third intercostal space demonstrates the mitral valve (AM) and left ventricular wall (LVW) echoes. Tilting the transducer superiorly to position 2 the atrioventricular wall (AVW) and left atrial wall (LAW) echoes are recorded. Recording the mitral valve from the fourth intercostal space (recording 3) record the LAW and not the LVW echo.

valve as a landmark (Fig 9 recording 2) In this way the transducer is directed superiorly enough from the third inter space so that the left atrium is always re corded Another advantage of the technique described in this study is the standardized approach utilizing several easily recognized landmarks. Standardization is an important consideration in all ultrasound techniques. First of all the easily identifiable mitral valve echo is used as a landmark in beginning the examination. Then by requiring the simultaneous recording of echoes from three different structures, interventricular septum atrioventricular wall and left atrial wall, the amount of variation from one examination to another should be minimized and the results should be quite reproducible The experience thus far tends to substantiate this point.

A major advantage of this ultrasound technique over routine chest roentgenograms in estimating the size of the left atrium is that a true internal left atrial dimension is obtained. Although this mea surement represents only one dimension of an ovoid-elliptical-shaped chamber the left atrium tends to enlarge in all directions, and one dimension should reflect any change in volume. For example, investigators have shown that for comparative clinical studies of left atrial volume left atrial angiograms taken only in one plane are as good as biplane examinations. The fact that the anteroposterior ultrasound dimension n this study correlated so well with the angiocardiographic determinations taken in the right anterior oblique projection supports the hypothesis that the left atrium enlarged in all directions at least to some extent.

There is some question whether the size of the left atrium is a function of body surface area. Murray and associates reported that there was no significant correlation between body surface area and left atrial volume calculated by biplane angiocardiography in normal persons. Castellanos and Hernandez however found a direct relationship between body urface area and left atrial area measured on the anteroposterior angiocardiogram The ultrasound measurements in this study demonstrated a statistical relationship with body surface area among the 21 normal subjects. Thus dividing the ultrasound left atrial dimension by body surface area narrowed the range among the normal subjects and facilitated the differentiation between normal and enlarged left atria.

The ability to obtain a good estimate of left atrial size in a very simple manner has several potential clinical uses. First of all such a measurement should be useful in the diagnosis of various cardiac abnormalities. Quantitative as well as qualitative evaluation of valvular lesions may be aided with such data. It has been demonstrated angiographically that in patients with aortic valve disease and primary cardiomyopathies the size of the left atrium correlates with the pressure in the left atrium [19] As a result this simple measurement may be helpful in evaluating the state of left heart compensation in these patients. Of course, with a measurement which is as simple and innocuous as this, it can be obtained frequently and as an outpatient if desired Therefore, it should be very useful in following either on a short or long term basis any cardiac abnormality in which a change in the size of the left atrium may influence the patient s management or prognosis.

Summary

A technique for estimating the size of the left atrium was developed using pulsed reflected ultrasound. The technique consisted of placing the transducer in the third inter costal space of the recumbent patient and recording echoes from the interventricular septum the atrioventricular wall and the posterior wall of the left atrium The distance between the atrioventricular wall and the left atrial wall echoes represented the left atrial dimension (LAD) This measurement was obtained on 21 normal subjects and 47 patients undergoing cardiac catheterization. Twenty-eight of these patients had selective left atrial cineangiocardiograms as part of their diagnostic workup

The correlation between the ultrasound LAD measurements and the size of the left atrium as determined by the cineangiocardiograms was excellent ($r = 0.9120$ $p < 0.001$) This estimate of left atrial size was better than was obtained with routine cardiac fluoroscopy Among the normal subjects the mean LAD was 3.1 ± 0.5 cm with a range of 1.8 to 4.0 cm. When divided

by body surface area the normal range was 1.2 to 2.0 cm per M.[2] The measurements on the 47 patients undergoing cardiac catheterization were consistent with known left atrial size in patients with various cardiac abnormalities. Patients with pure mitral valve disease or bivalvular disease had constantly high LAD measurements. The measurements were smaller but still usually abnormal in patients with pure aortic valve disease and were normal in patients with atrial septal defects.

The advantages of this ultrasound technique over currently available methods for estimating left atrial size are convenience and accuracy. The examination eliminates the hazards and inconvenience of angiocardiography and by obtaining a true internal dimension of the left atrium rather than merely visualizing one or two of the chamber's external borders, this procedure is more accurate than routine cardiac fluoroscopy and chest roentgenograms.

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A neurologic grading system for acute strokes

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In the past, a number of criteria have been proposed for assessing the severity of and predicting a possible death from a coronary episode. Some have assigned a numerical index to certain factors, while others using various criteria have classified patients as mild, moderate, and severe. Lown and associates[1] have urged a consensus on a system of grading myocardial infarctions for the purpose of comparing data from different coronary care units.

A similar type of index for acute stroke patients should be of value. There has been a recent upsurge of interest and activity in all aspects of the stroke problem ranging from the application of intensive care to various medical and surgical modes of therapy. The grading system described below has been useful in our hands in predicting deaths. We would anticipate that it may also allow for more meaningful comparison of results of various medical and surgical therapies than now exist.

Materials and methods

Since October, 1966, a Stroke Intensive Care Unit has been in operation at St. Francis General Hospital in Pittsburgh through a grant from the United States Public Health Service. To test the efficacy of this approach, stroke patients from two other local community hospitals are being followed as controls. Their diagnoses included cerebral thrombosis, embolism, and subarachnoid and intracranial hemorrhage. All patients have neurologic deficits. Patients with transient cerebral ischemic attacks are excluded from the study.

In an attempt to better evaluate the stroke population at the three hospitals, a grading system based solely on the initial neurologic deficit was used. This system was slightly modified from one kindly supplied to us by Gilroy and co-workers[2] who used it in 1963 to evaluate the use of papaverine in acute stroke victims. We are in agreement with them that this system has been simple and accurate, and the results could be easily duplicated by different examiners familiar with the routine neurologic examination.

Each patient was seen by one of the authors (J. E. T. or T. J. P.) and underwent a general examination as well as a detailed neurologic examination which was recorded on a standard form. The patients in all three hospitals were examined within 48 hours of the completion of their stroke and at that time were given a grade. They were then followed for 30 days or until their death, if that occurred first.

From the Stroke Intensive Care Unit of St. Francis General Hospital, Pittsburgh, Pa.
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Table I. Stroke study neurologic evaluation

Mentation	
11 Normal	5 Aphasic
10 Orientated but lethargic	4 Severe general disorder of mentation
9 Orientated but d phasic	3 Stuporou
8 Disorientated	2 Semicomatosed
7 Disorient ted nd leth rg	1 Comatosed
6 Disorie tated nd dy pha	0 Death
Motor	
11 Normal	5 Monoplegia
10 I ol tary movement r d t nia (m ld)	4 Severe cerebellar ta i
9 Monoparesis	3 Quadriparesi
8 Mild cerebella taxia	2 Hemiplegia
7 Hemiparesi	1 Quadriplegia
6 I ol tary movement r d t nia (severe)	0 Death
Cra ial nerv	
11 Normal	5 Paralysis extraocular movement
10 Inatte t n hemianopia	4 Dy phagic
9 Centr l or peripher l 7th paral	3 Respirat ry arrhythmia or semicoma
8 Paresis extraoc lar movement	2 Akinetic m tism
7 Hemianopia	1 Apne or coma
6 Dysarthric	0 De th
Sensation	
6 Normal	2 Respond only to pa nf l stim li
5 U ilateral sensory deficit (m ld)	1 No response t painf l t muli
4 U lateral sensory deficit (severe)	0 De th
3 Bilateral sensory deficit	
Reflexes	
5 Normal	2 Bilateral extensor plantar
4 Asymmetrical DTR	1 B later l absent plantar
3 U ilateral extensor plantar	0 De th

Note When more than one cond tion present in same category check item with lowest score in that subgroup

Modified from John Gilroy M D

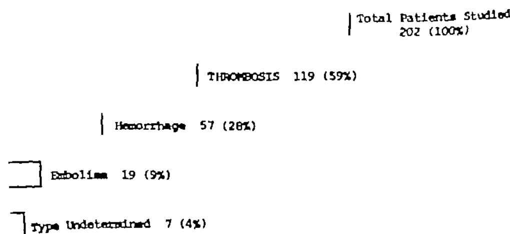


Fig 1 Types of stroke among 202 consecutive patients, August 1967 through April, 1968

The grading system is shown in Table I The mechanics of this system depend on subdividing neurologic findings into five categories (1) mentation (2) motor (3) cranial nerves (4) sensation and (5) reflexes. The patients were given a grade based on the most severe deficit in each category The numbers in the five categories were then tallied and this was the patient s overall and final score. The patient with no neurologic deficit received the highest grade of 44 and the dead patient received a grade of zero In order to be included in the study however all patients had to have a neurologic deficit or a bloody spinal fluid

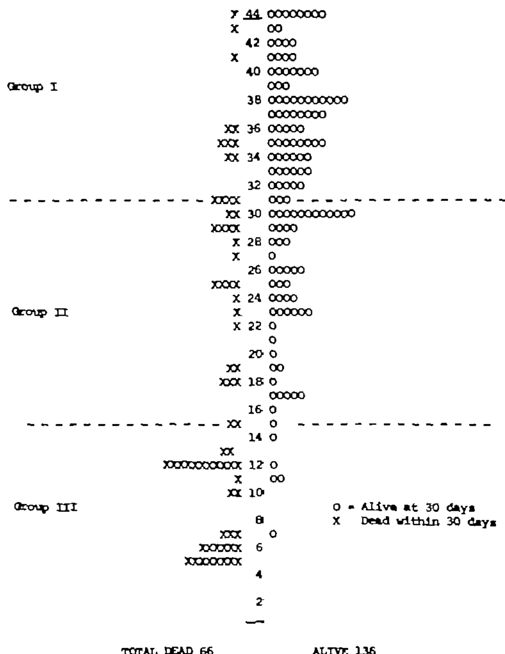


Fig 2 Neurologic score in 202 acute stroke patients.

Results

The distribution of the types of strokes encountered in the 202 consecutive patients studied from August 1967 to April 1968 is shown in Fig. 1. The vast majority of patients fell under the category of thrombotic and hemorrhagic strokes. The small group of patients labeled "Type undetermined" were those in whom the clinical and laboratory data did not allow us to make a clear statement regarding etiology. Hemorrhagic strokes encompassed both subarachnoid and intracranial hemorrhages.

The 202 patients studied in this series were arranged in a scattergram fashion as demonstrated in Fig. A total of 66 out of the original 202 patients died within 30 days for an overall mortality rate of 32.6 per cent. It is readily apparent that the patients with a low neurologic score fared much poorer than those with a higher score. From inspection we subdivided the total group of patients into three categories according to their neurologic score. The patient with a score between 32 and 44 made up Group I, those with a score between 16 and 31 were designated as Group II and those with a score of 15 or less comprised Group III. Table II gives the distribution of the types of stroke occurring in each of the three groups. Of the 42 patients in Group III 86 per cent were dead within 30 days whereas only 11.5 per cent of Group I patients were dead at the same period of time. The 73 patients in Group II had an overall mortality rate of 37 per cent.

After examining the distribution of the ages of the three groups of patients (Fig. 3) it was observed that the patients in Group I had a younger age distribution ($p < 0.05$ per cent) than those in Groups II and III. However, it is also apparent that the age distribution of Groups II, III were very similar and therefore it is likely that the observed differences in mortality rates in the three groups of patients could not be explained solely on the basis of the age differences noted. Application of the grading system to larger numbers of patients should clarify the influence of age.

A chi square test for the homogeneity of the death rates in the three groups determined at the 5 per cent level that the observed differences were not due to chance. We then adjusted the scores for age and diagnosis by a regression technique using diagnosis and age as independent variables and the observed score as the dependent variable. The two-sample Kolmogorov-Smirnov Test was applied to examine whether the distribution of the age-adjusted scores for the alive and dead groups were different. As the test was significant ($p < 0.05$ per cent) we concluded that the scores were significantly different. The results of these tests permitted us to say that if patients of the same age group and diagnosis were compared, their score would be a fairly accurate indicator of their life and death prognosis in the first 30 days following a stroke.

Conclusion

We have presented our initial experience with a neurologic grading system for acute strokes. Patients have been placed into

Table II. Categories of stroke in 202 patients related to neurologic score (numbers in parentheses indicate percentage of the total number in that score grouping)

Score	Group III (15 pt or lower)	Group II (16 to 31 pt)	Group I (32 to 44 pt)
Thrombosis	11 (26%)	50 (69%)	56 (64%)
Hemorrhage	27 (65%)	10 (13%)	22 (25%)
Embolism	1 (2%)	11 (15%)	7 (9%)
Type undetermined	3 (7%)	2 (3%)	2 (2%)
Total	42	73	87

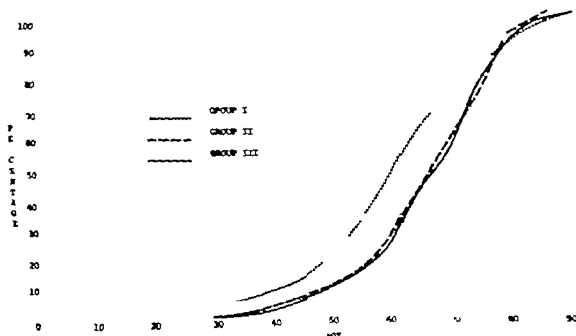


Fig. 3. Age distribution for each score group.

three groups depending on their numerical score and thus has proven to have predictive value regarding acute phase prognosis.

Widespread utilization of a grading system of this type will allow for more meaningful and objective evaluation of results of medical and surgical treatment from various institutions.

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The cardiac pacemaker

Effects of regularly spaced nervous input

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It has been demonstrated in a neural model and in two biologic situations that certain conditions will cause an increasing frequency of inhibitory neuronal input to produce an acceleration of output from a pacemaking cell above the rate produced by lower frequencies of inhibition. In the neural model the logical converse was also demonstrated: increasing the frequency of an excitatory input could produce deceleration of a pacemaker cell so that it discharged at rates lower than those resulting from lower frequencies of excitation. Under the proper conditions, the paradoxical response to inhibitory input is brought about by "locking" the pacemaker to the input frequency so that it discharges in a fixed ratio. As the input frequency changes, the locking remains until the pacemaker rate breaks free. It may then lock at a different ratio. Thus a series of zones can be found during which the paradoxical response occurs, but between which the pacemaker frequency will change in the normally expected direction. The longest and clearest zone occurs at a 1:1 ratio. In conformity with Perkel and associates,[1] these zones will be called "stable zones" in this report.

The phenomenon of locking the heart rate to the frequency of vagal stimulation was observed incidentally in the course of other studies, and it seemed profitable to examine the phenomenon in greater detail, since cardiac rate is normally in the region of the physiologic frequency of autonomic motor nerve impulse transmission.

Methods

Cats were anesthetized with sodium pentobarbital 30 mg. per kilogram intravenously; in rats (Wistar strain) the dose was 45 mg. per kilogram intraperitoneally. The chest was opened by a sternal splitting incision and the animal was respired through a tracheostomy. The right and left stellate ganglia and their emerging cardiac branches were gently defined for later stimulation or decentralization or excision. Decentralization was accomplished by cutting the sympathetic chain just below the stellate ganglion and cutting the contribution of the first thoracic preganglionic sympathetic efferent. The vagi were isolated in the superior mediastinum and placed on platinum electrodes. Leads from the right front and left rear legs were used for recording the electrocardiogram on a two channel direct writing recorder. Stimulation was provided by monophasic square-wave pulses of 2 msec. duration (which were found to give maximal response) and by pulses of supramaximal voltage through radioisolation units. The supramaximal voltage was found by increasing voltage until maximal cardiac rate re-

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sponse was observed and then increasing further by 5 volts the result was in the range of 12 to 17 volts.

A complete experiment on a single animal was as follows vagal stimulation was begun at low rates with both the vagal and sympathetic innervation intact. The stimulation rate was slowly increased until locking was first obtained usually in a 2 1 ratio of sinus pacemaker vagal stimulation frequency (In this report all ratios are quoted in the same order) The stimulus was then discontinued and after the return of the pacemaker rate to the base line restarted When locking had been recorded the stimulus was again discontinued until the pacemaker rate returned to the base line Stimulation was then begun again at 1 to 2 pulses per minute higher frequency Locking might now still be obtained or might not. This cycle of activities was continued until locking at that ratio was no longer obtained as the stimulus frequency was increased After a stable zone had been defined in this way the stimulus frequency was returned to the lowest frequency at which locking was obtained and following a period of non stimulation to allow return of the pacemaker to its basal rate the stimulation was begun again As soon as locking was obtained the stimulation frequency was slowly and continuously increased to above the rate which had previously been defined as the maximum for that stable zone. The stable zone was therefore defined in two ways first by discontinuous and then by continuous increase in vagal stimulation frequency

In early experiments the start of the next stable zone was then identified by gradual discontinuous increases in stimulation frequency In later experiments in order to save time the start of the next stable zone was identified by continuous increase in vagal stimulation frequency The whole cycle of activities relevant to a stable zone was then repeated In such a way progression through stable zones at decreasing ratios was achieved until the 1 2 or 1 3 ratio had been studied

At this point either the vagi were de-



Fig 1 Graph of atrial rate vs vagal stimulation frequency for single cat. Filled circles Vagi and stellate ganglia intact. Unstimulated atrial rate 144 per minute. Crosses Vagi decentralized. Unstimulated atrial rate 150 per minute. Open circles Vagi and stellate ganglia decentralized. Unstimulated atrial rate 1 4 per minute. The stable zones appear as straight lines during which atrial rate follows vagal stimulation rate in simple ratios.

centralized or the stellate ganglia were excised or decentralized and the whole procedure was repeated

Finally both vagal and sympathetic central connections were removed and the procedure repeated again A number of experiments that did not follow the total protocol were performed so that individual features could be studied in depth while the preparation was still fresh

At the end of each experiment the vagi were crushed at points on their courses between electrodes and heart without disturbing the electrodes Stimulation then had no effect on the heart confirming that stimulation was through these nerves and not by direct electrical conduction In those experiments where attempts were made to obtain locking to sympathetic nerve stimuli the cardiac branches at their emergence from both stellate ganglia were placed on the electrodes, the procedure being identical with that described for vagal stimulation

Reserpine was given as Serpasil (Ciba) intraperitoneally Doses given were either 1 mg per kilogram daily for 2 days, 0 5 mg per kilogram for 3 days or 0 2 mg per kilogram for 4 days, in each case the last dose being 24 hours prior to the experiment

Results

Experimental findings cats Vagal stimulation slowed the sinus pacemaker the phenomenon of locking was observed when there was a simple ratio of pacemaker rate stimulus frequency Fig 1 illustrates the results in a single preparation locking occurred at a number of ratios over appreciable ranges of frequency and the stable zones thus identified are seen as straight lines which if extended would pass through the 0-0 coordinates. During these stable zones, increase in vagal frequency results in higher sinus pacemaker rates Fig 2 shows excerpts from a continuous trace defining a stable zone

Stable zones of 2 1 3 2 1 1 2.3 1.2 and 1 3 ratio of sinus pacemaker vagal stimulus frequency were observed (Figs. 3 through 7) At a 1 1 ratio the sinus pacemaker rate could be increased in most cases by 5 to 11 beats per minute the maximum was 37 beats per minute. At the 2 1 ratio the greatest increase observed was 4 beats per minute at a 1.2 ratio 8.5 beats per minute When the vagi were decentralized by section in the neck, the stable zones were sometimes slightly extended and if the stellate ganglia were excised or decentralized and a lower spontaneous rate obtained the stable zones were prolonged by 5 to 10 beats per minute

Prior treatment of cats with intraperitoneal reserpine produced observable differences. The stable zones were shorter than in untreated animals, but stellate ganglionectomy still extended them.

When locking occurred it was unmis-

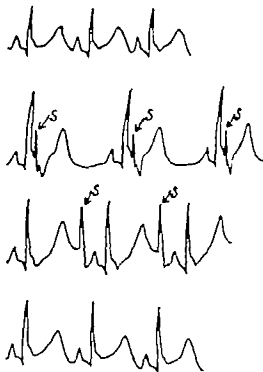


Fig 2 Four consecutive excerpts from continuous trace. The uppermost and lowermost electrocardiograms were taken before and after period of vagal stimulation in which the rate of stimulation was continuously increased. The second excerpt shows the lowest rate (118 per minute) at which 1 1 lock was first obtained. The third, taken 78 seconds later shows the highest rate (146 per minute) Stimulus artifacts appear in these two traces, identified as S Electrocardiogram in this and other figures have been retouched for photographic purposes. Time interval 1 second. Subject cat.

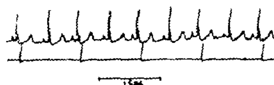


Fig 3 Lock in 2 1 ratio. Vagal stimulation, cat. 1 Figs. 3 through 8 the top lines are the electrocardiograms, the bottom lines, records of the stimuli. The stimuli may also be seen as artifacts in the electrocardiograms. Rhythm is sinus rhythm in all figures.

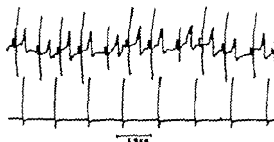


Fig 4 Lock in 3 2 ratio. The rhythm is characteristic of the ratio. Vagal stimulation, cat

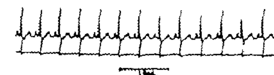


Fig 5 Lock in 1 1 ratio Vagal stimulation, cat



Fig 6 Lock in 2 3 ratio. Vagal stimulation, cat.

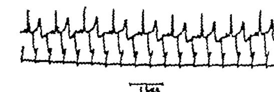


Fig 7 Lock in 1 2 ratio Vagal stimulation, cat

takable due to the rhythmic clicking of the recorder pens. Several phenomena in conjunction with locking were noted

1 Continuous and discontinuous increase in vagal stimulation rate defined stable zones that were usually identical as long as the rate was slowly changed during continuous increase of vagal stimulation frequency The slow rate was a change of about 5 pulses per minute during 10 seconds. Rapid change (e g 5 pulses per minute during 2 seconds) invariably broke the lock. Fig 2 shows the effect of continuous slow change in stimulation frequency

2 On either side of the range of frequencies producing fixed prolonged locking transient periods resembling locking could be obtained. To be certain of locking therefore it was necessary to record it for several minutes and to obtain a range of frequencies at which locking occurred for a particular ratio Occasionally complex ratios (e.g 5.3) were obtained over prolonged periods, but a range could rarely be determined

3 The stimulus tended to fall at a particular point in the electrocardiographic complex for a particular ratio and frequency For example in Fig 3 the point lies in the S-T interval. This locking point was not rigidly fixed in recordings over 10 minutes or more it could be seen to wander within narrow limits, over a range of at most 100 msec

4 The locking point for different frequencies and ratios was predictably sited When vagal frequency was being increased and a 2 1 or 1 1 ratio was first obtained the point was invariably in the S-T segment about 170 msec. after the peak of the P wave. With further increase in frequency the point fell earlier and earlier in the complex when it coincided with the onset of the P wave a higher stimulation frequency would no longer elicit locking—the upper limit of the stable zone had been reached. These features are shown in Fig 2

5 When locking occurred at a 1.2 ratio of pacemaker vagal stimulus frequency the vagal volleys fell in the S-T and T P intervals (Fig 7)

6 Cats varied in their sensitivity to the effects on pacemaker rate of a single vagal

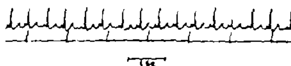


Fig 8 Arrhythmia due to vagal stimulation at a rate slightly less than that producing 1 2 ratio Vagal stimulation at [illegible]

volley The greater the response to a single volley the longer were the stable zones obtained in that preparation

7 The maximal rate to which the pacemaker could be driven in a stable zone was always below the spontaneous rate of the pacemaker

8 Arrhythmias very like respiratory sinus arrhythmia could be produced by stimulation frequencies near to those which elicited locking (Fig 8)

Experiments were carried out designed to elucidate the basis of these particular findings.

Very low frequency stimulation (e g 10 pulses per minute) allowed analysis of the effects on the pacemaker of vagal volleys arriving at different phases of the electrocardiographic cycle Certain relationships were established delay between stimulation and volley arrival being considered negligible The findings can also be observed in Figs. 4 and 8 although in these figures stimulation was at higher rates.

1 Arrival of a volley in the period between a P wave and a point usually corresponding with about the T peak produced well marked prolongation of the P P interval that started during this period The prolongation was maximal when the interval between the P wave and the moment of arrival of the volley was about 170 msec. the arrival being in the S-T interval little or no prolongation of the next P P interval occurred when a volley arrived during this same period

2 Arrival of a volley after about the end of the T wave produced no effect on the P P interval that included the T wave In different animals the end of the T wave came between 200 and 400 msec after the preceding P wave The next P P interval was minimally prolonged when the volley arrived shortly after the end of a T wave.

3 In any one preparation the nearer the P wave that the volley arrived in the T P interval the greater was the effect on the next P P interval The effect was maximal when vagal stimulation occurred at the onset of the P wave

Attempts to obtain locking to bilateral accelerator nerve stimulation were rarely successful whether the vagi were intact or not and whether the stellate ganglia were decentralized or not Transient lock would be obtained but after 15 to 30 seconds of stimulation the pacemaker would wander out of lock In distinction from vagal stimulation sympathetic stimulation did not usually produce a fixed rate of pacemaker activity the pacemaker rate tending to vary slowly in either direction even after prolonged stimulation

Single volleys through the accelerator nerves produced minor changes in cycle length again in distinction from vagal effects. When locking to a particular frequency was obtained however no stable zone could be determined either at 1 2 or 1 1 ratio

Experimental findings rats The same general findings were obtained in rats as in cats with certain quantitative differences. The pacemaker was so sensitive to vagal volleys that locking ratios of 2 1 and 3 1 were easily obtained Clear stable zones were therefore short because with slight increases in the vagal stimulation frequency the ratio would immediately change with a marked decrease in pacemaker frequency Moreover when a lock was obtained e g at a 1 1 ratio the pacemaker was frequently most irregular P P intervals varying from short to long although the ratio was maintained This was an exaggeration of the slight wandering of the locking point described for cats as the third phenomenon observed in conjunction with locking to vagal stimulation

Discussion

The resemblance of the present results and especially Fig 1 to those reported by Levy and associates suggests that the condition necessary for manifestation of the locking phenomenon occur at the cardiac pacemaker This implies, among other things that the disappearance of the

changes in potential brought about at the sinus pacemaker by a vagal volley is exponential.

The differing effect on the P-P interval of single vagal volleys, arriving at different times in relation to the P wave presumably underlies the finding that locking points change with changes in vagal stimulation frequency. At the lowest and highest frequency of a stable zone locking can be expected only if the effect each volley produces is timed to be sufficiently effective. Therefore the range of locking points lies between the P wave and a later point, which happens to be in the S-T period in the cat. At the lowest frequency a second vagal stimulus will fall at the furthest point from the first at which the sufficient effect of the second stimulus can be obtained, i.e. in the S-T period whereas at highest frequency the second stimulus will fall next at the nearest point and so coincide with the P wave.

A finding that requires explanation is the range over which single volleys produce maximal effect and during which locking occurs. As described previously this range terminates at 200 to 400 msec. in different cats after the peak of the P wave, a point usually close to the peak of the T wave. It may be related to the period of sinus node depolarization since it has been shown in the rabbit that electrical shocks, delivered towards the end of the period of depolarization delay the following depolarization more than those delivered nearer the beginning. During the interval between the terminal point and the onset of the next P wave timing of that P wave is not altered by vagal action; the subsequent P wave however is delayed. The best inference is that there is a delay between stimulation and vagal effect equivalent to a T-P interval roughly 100 msec. of which only 10 msec. at most can be ascribed to nerve conduction.

The results may be significant not only for the interpretation of non-expiratory sinus arrhythmias in man but also in a number of other ways. They point to the possibility that the significance of dual innervation of the pacemaker is not only that it provides more sensitive control but also that it prevents entry to or prolongation of stable zones so that at all frequencies activation of the nerves will tend to produce the same type of response. It is interesting in this connection that pacemaking smooth muscle has dual innervation. The extents of sympathetic and vagal activation under the conditions of the experiments are shown by the changes in cardiac rate that follow the excision of these nerves.

Also the possibility arises that feedback control of autonomic motor nerve impulse frequencies in relation to pacemaking frequencies may be important. In the present experiments, excision or decentralization of the stellate ganglia could have decreased the possibility of information being carried centrally to the cardiac control center in the medulla; it did extend the stable zones even after prior reserpine treatment. The same effect was seen though not regularly from vagal section in the neck cephalad to the site of stimulation. Thus the information from heart to baroreceptors that is significant may be not only the level of arterial blood pressure but also the frequency and exact timing of the heart beat. Since also the baroreceptor response to systolic rise in arterial pressure may reflexly activate the vagus nerve within the period of one cardiac cycle it is theoretically possible for a rise in heart rate to cause, in a stable zone, a further rise in heart rate which situation dual innervation would be able to prevent. A breakdown in such mechanism at any level from receptor to effector would result in faulty regulation of the pacemaker.

Summary

Experiments were conducted to see if the observations reported by Perkel and associates could be extended to the cardiac pacemaker. In anesthetized cats and rats, the pacemaker responded to regularly spaced vagal stimuli in simple frequency ratios over appreciable ranges of frequency. Within these ranges, increase in vagal frequency caused increase in pacemaker rate. Between the ranges response was orthodox. Vagal or sympathetic decentralization extended stable zones, reserpine pretreatment reduced them.

The point in the electrocardiographic cycle at which the stimulus fell during a

period of fixed ratio changed predictably. This change accorded with and is explained by the effect of individual stimuli arriving at different times in relation to the P wave on the sinus pacemaking rate.

Fixed ratios but no ranges were demonstrated with sympathetic stimulation.

Dual innervation may serve to prevent paradoxical responses and monitoring of pacemaking may play a physiologic part in determining frequency in nerves controlling the pacemaker.

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Transcutaneous directional flow detection

A preliminary report

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The pattern of the oscillatory flow observed in the arterial system is dependent upon the heart as well as the location of the artery, its size, the resistance of the bed it supplies, and the physiologic conditions under which the observations are made. The flow curve recorded from the major artery supplying the vascular beds of relatively high resistance consists of a large systolic forward flow component which is immediately followed by a brief period of flow reversal. A second small forward flow component may occur prior to the next pulse cycle (Fig. 1). In regions of low vascular resistance such as the brain, liver, and kidneys, there is usually a much larger mean flow component without flow reversal.

Information relative to the oscillatory flow pattern has been recorded in animals with the electromagnetic flowmeter which permits a recording of instantaneous velocity and flow direction. Although the electromagnetic flowmeter has been extensively applied in animal studies, it has limited application in man because it requires (1) operative exposure of the vessel, (2) it is not easily used on veins, and (3) the anesthesia which is required, depending on the type used, may profoundly influence cardiovascular dynamics.

The need for accurate measurement of the directional components of arterial and venous flow has been obvious to the physiologist who is interested in describing the physical behavior and characteristics of the circulation. The demand or need for similar information in clinical medicine has not been as apparent except as it relates to the determination of average volume flow.

Our interest in the prospect of studying both instantaneous velocity and direction of flow was stimulated by observations made with the transcutaneous ultrasonic velocity detector. This instrument provides qualitative information relative to

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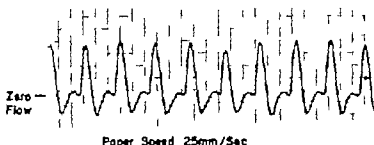


Fig. 1. The flow pattern of the femoral artery shown is typical of the type observed when there is a small amount of retrograde flow.

flow velocity but cannot differentiate between forward or reverse flow. It soon became apparent from studying arterial and venous flow patterns in various disease states that in many situations flow reversal was undoubtedly occurring. Our inability to accurately define the direction of flow hampered our interpretation of the data.

The purpose of this report is to present our initial experience with a prototype directional velocity detector and suggest some potential applications. While our observations are preliminary, the data may be sufficiently interesting and exciting to encourage others to utilize this technique.

Instrumentation

High frequency sound waves which are reflected from the moving particles in blood are shifted in frequency by an amount proportional to flow velocity. Early implantable and transcutaneous velocity detectors utilizing this Doppler or shift frequency were unable to distinguish flow direction because of their inability to discern between positive and negative frequency shifts. The analogue output of such a system portrayed all flow motion in one direction only.

The possibility of detecting flow direction became feasible with the development of a circuit by one of the authors (F. D. McLeod).* This device introduces a phase shift prior to detection, making possible the identification and separation of positive and negative Doppler shifts.

A beam of low intensity 10 megahertz ultrasound is coupled through the skin to the blood stream. A small portion of the ultrasound is scattered and returned to a receiving transducer. The scattered sound experiences a frequency or Doppler shift proportional to the flow velocity.

The sound scattered from a flow component can be expressed as

$$F = 1 \cos 2\left(f + \frac{f\,1}{C}\right)t$$

where f is the transmitted frequency, C is the velocity of sound in tissue, 1 is the velocity of scatter.

The Doppler shift $\frac{f\,1}{C}$ is obtained by separately multiplying E by $\cos 2\pi ft$ and $\cos(2\pi f + \phi)$ since

$$\cos\alpha \cos\beta = \tfrac{1}{2}[\cos(\alpha + \beta) + \cos(\alpha - \beta)].$$

Thus

$$E_A = 1 \cos 2 \frac{f\,1}{C}$$

$$E_B = A \cos 2\pi \frac{f\,1}{C}\, t + \phi.$$

Depending on the sign of 1, which indicates forward or reverse flow, the phase shift ϕ either adds to or subtracts from the Doppler shift. The non-phase-shifted signal E_A is used as a reference for determining the sign of ϕ.

The phase shift ϕ and thus the phase relationship of E_A and E_B is easily determined by listening to the signals on stereo headphones. A simple logic circuit is used to combine E_A and E_B to produce voltages proportional to the mean forward and reverse velocity components. These voltages can be recorded separately as forward and reverse velocity or differentially as mean velocity. This instrument in its present stage of development cannot be used to measure volume flow.

*Manufactured by Parks Electronics Laboratory, Route 2, Box 35, Beaverton, Ore. 97005.



Fig. 2 The surge of flow in vein directly overlying an artery is in the opposite direction and so indicated by the directional velocity detector. With the nondirectional device, all flow changes are depicted as positive deflections.

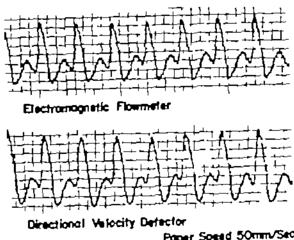


Fig. 3 A comparison of the type of wave forms recorded with the electromagnetic flow meter and the directional velocity detector shows that the outputs are nearly identical.

Methods and results

In this study we have evaluated the following aspects of the directional velocity detector: (1) testing of its directional capabilities under conditions where we are certain flow direction is changing; (2) determine the type of data presentation that provides the greatest amount of information; (3) survey the peripheral arteries and veins of five normal subjects; and (4) examine patients in whom directional flow changes could be of some importance.

Directional capabilities. The simplest test of the directional capability of the instrument is to record velocity changes from an area where an artery and vein are superimposed. One location where this can be easily tested is the antecubital fossa where the antecubital vein lies anterior to the brachial artery. With the transducer directly over the two vessels and depressed slightly to partially occlude the vein, only the arterial signal is recorded. When the fist is clenched, the venous flow is suddenly increased in velocity to a detectable level past the overlying probe. When this occurs the directional flowmeter output shows the surge of venous flow to be in the opposite direction to arterial flow. A comparison of this output with that obtained with the nondirectional instrument is shown in Fig. 2. For the type of analogue record shown in Fig. 2, the output of the two zero-crossing circuits for forward and reverse flow is combined in a differential amplifier.

A further test of the directional velocity detector was made by comparing its analogue output with a square-wave electromagnetic flowmeter.* These studies were made on the femoral artery of the dog with

*Manufactured by Statham Research Corporation, 8901 West Imperial Highway, Los Angeles, Calif. 90045.

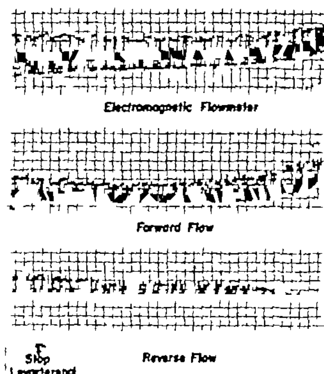


Fig 4 The information relating to forward and reverse flow in a femoral artery in a dog has been recorded on separate channels. With this type of presentation the time-course changes may be more accurately depicted. When the levarterenol infusion was stopped the peripheral resistance decreased, mean flow increased, and reverse flow gradually disappeared

the transcutaneous probe placed one centimeter distal to the electromagnetic flow probe. A 1 F 90 catheter was placed in a side branch of the artery distal to both velocity detectors and used for infusion of levarterenol which increases peripheral resistance and accentuates the amount of flow reversal

When the outputs of the two zero-crossing circuits of the directional flowmeter were combined they provided a wave form which was nearly identical to that obtained with the electromagnetic flowmeter (Fig 3). The zero flow points determined by arterial occlusion while not shown on this record were nearly identical in position on both flowmeter outputs.

When the forward and reverse flow components of the oscillatory cycle were presented on separate channels, the information appears more meaningful. This is evident in Fig 4 which shows the time course of events when the levarterenol infusion was stopped. As the reverse flow tended to decrease there was a definite increase in the mean forward flow as evidenced both by the changes in the electromagnetic flowmeter output and the forward flow channel.

Method of analogue presentation With the prototype instrument there are three methods of presenting the forward reverse flow information. A single channel can be used with forward and reverse flow being examined by a switching arrangement. This is not satisfactory since it does not permit a continuous record of either nor does it allow precise timing of the two events as they relate to one another

As shown earlier combining the two outputs gives a velocity recording nearly identical to that observed with the electromagnetic flowmeter. This has been the standard method of presenting flow information but it does have some limitations. When the information for both forward and reverse flow is combined the recorded wave form may not clearly indicate the pattern of flow as it is actively occurring. This can

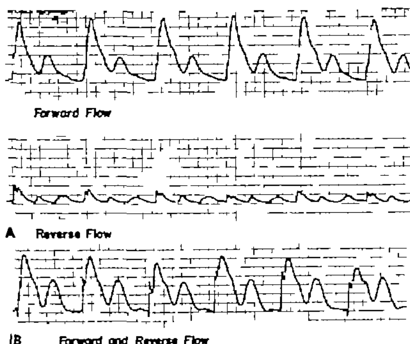


Fig 5 A The differences in the type of information that can be obtained when the forward and reverse flow in brachial artery (aortic insufficiency) are presented on separate channels It would not be possible to suspect the changes in direction that are occurring if the combined output alone used B When the outputs of the zero-crossing circuits are combined, the recorded wa form bears little resemblance to the events as depicted in A

be shown by closely examining Fig 5 These recordings were made from the same subject and the same artery w th the only difference being in the method of displaying the information The wave form obtained by the combined outputs represents the average velocity at a particular time in the cardiac cycle without accurately portraying the actual time course of events relative to forward and reverse flow From the records in Fig 5 it can be seen that flow reversal is actively occurring at times when there is still net forward flow a fact not appreci ated by the combined output of the two zero-crossing circu ts of the ultrasonic de vice It is probable that a similar type of output would be expected with the electromagnetic flowmeter

Clin cal studies In normal subjects flow reversal can and does occu *as far periph er lly* as the radial and posterior t l al arteries, but this is not on tant find ng In large veins, the size of the common femoral, flow is normally phasic with respiration and does not cha ge direction

We have investigated a number of con ditions in which flow reversal might occur

1 ARTERIOVENOUS FISTULA We studied the velocity pattern in the cardiac artery *of two side-to-side arteriovenous fistulas* (radial artery vein) that had been constructed n the arm for use in chronic renal dialysis. Since the fistula empties into the very low resistance venous system flow reversal would not be expected and indeed this was the case However when the fistula was acutely occluded some dramatic changes in the velocity patterns occurred (Fig 6) There was n abrupt decrease in the mean flow component w th the prompt appearance of flow reversal With release of fistula compression the reverse flow promptl disappeared

2 CARDIAC DISEASE. There are several aspects of the circulation *that might be* n estigated w th a directional flowmeter Th ost obvious s the patient w th aortic regurgitatio n An example from tl brachial tery is own n Fig 5 The formation recorded on th reverse flow channel repre

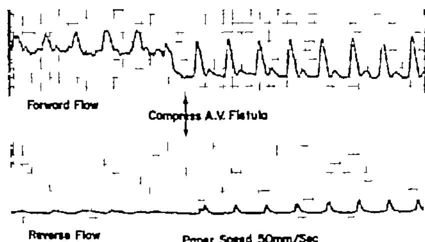


Fig 6 When the flow through the side-to-side radial brachial artery vein fistula was suddenly stopped by compression, there was an immediate decrease in the mean flow and the prompt appearance of reverse flow. The opposite pattern was observed with release of the fistula compression.

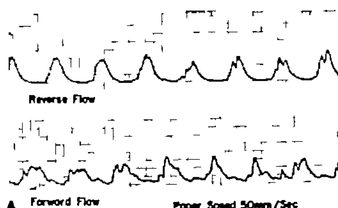


Fig 7 A The recording made from the common femoral vein in a subject with severe mitral regurgitation and heart failure. There is both forward and reverse flow depicted.

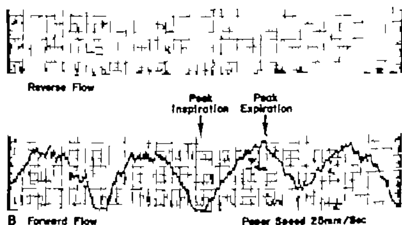


Fig 7 B After correction of the mitral regurgitation with relief of the severe heart failure the femoral venous flow velocity pattern lost its pulsatile quality. There was no flow reversal noted at any point in the respiratory cycle.

sents a more complex series of events than was anticipated. Flow reversal is occurring during events in the cardiac cycle that seem highly improbable but identical records have been obtained on the three patients tested. This will be considered in more detail in the discussion.

In previous studies with the nondirectional velocity detector we noted that patients in congestive heart failure had very abnormal venous flow patterns. Instead of varying in frequency with respiration alone the velocity signal was often continuous with superimposed pulsations. An example



Fig. 4. A. The venous velocity tracings from the right common femoral vein were made from a patient in severe congestive heart failure secondary to mitral regurgitation. The flow reversal appeared to coincide with right atrial contraction and the rise in femoral vein pressure.

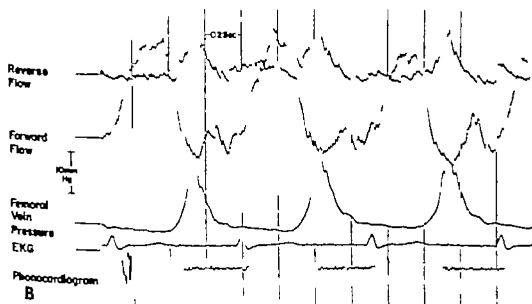


Fig. 4. B. The tracings are from a patient with advanced tricuspid insufficiency. The reverse flow component recorded from the femoral vein coincided in time with right ventricular contraction.

of the venous flow pattern recorded with the directional device is shown in Fig. 7, A. As can be seen, there is both forward and reverse flow in this patient with severe mitral regurgitation and heart failure. Flow could be stopped by a Valsalva maneuver. Two weeks after open heart surgery with correction of the defect, the venous velocity pattern was entirely normal, losing its pulsatile nature and varying in frequency only with respiration (Fig. 7, B).

In order to obtain the maximum amount of information relative to the venous flow patterns in heart disease, it is desirable to combine the velocity information with pressure recordings and the electrocardiograph. This permits accurate timing of the flow reversal as it pertains to pressure changes and events during the cardiac cycle. When the recordings illustrated in Fig. 7, A were made on a multichannelled recorder (Electronics for Medicine) along with femoral vein pressure and the electrocardiogram, some interesting relationships became apparent. As noted in Fig. 8, A, reverse flow appeared to coincide with the rise in femoral vein pressure, which in turn could be associated with right atrial contraction.

A completely different time course relationship between forward and reverse flow in the venous system is illustrated in Fig. 8, B. This patient had far advanced tricuspid insufficiency. The femoral vein pressure rise and reverse flow appeared to correlate with the electrical events that corresponded to right ventricular contraction.

3. ARTERIOSCLEROSIS OBLITERANS. In the 15 patients studied, flow reversal was not observed distal to areas of occlusion, but was noted in some cases in the vessels proximal to the area of involvement.

Discussion

Most of our information relative to flow patterns in peripheral arteries and veins has come from experimental animal observations, usually in the dog, where it is possible to apply the available flow measuring devices. In general, flow reversal in the arterial system has been described in the large arteries such as the thoracic aorta, abdominal aorta, and femoral artery. The extent of the flow reversal observed in these vessels has been greatly influenced by the vasomotor tone, being increased by vasoconstriction and decreased by vasodilatation. The retrograde flow is not thought to occur in the more peripheral arteries such as the saphenous artery of the dog.

Studies related to the human circulation with regard to flow reversal are sparse for obvious reasons. Attempts have been made to relate the findings in animal studies to the awake human but, as is often the case, the correlation is risky. It is now becoming obvious that valid observations pertaining to normal and disease states should wherever possible be made in the human.

The information derived from the directional velocity detector, while still qualitative, opens up entirely new areas for clinical investigation. Since the technique is safe, painless, and repeatable, it is possible to examine the flow patterns from many levels of the arterial and venous circulation.

At first glance it would seem desirable to express the output of the directional device as one composite wave form showing the algebraic sum of both forward and reverse flow, which resembles the type obtained with the electromagnetic flowmeter. The electromagnetic flowmeter now appears to be the best established method of accurately recording pulsatile flow. These early observations suggest a disadvantage in using an output which examines the mean instantaneous flow because it appears that such an output *does not* accurately portray the timing relationships of the forward and reverse components of flow. In examining the published flow records made with an electromagnetic flowmeter, backflow would appear to begin at the end of systole. Our studies with the directional velocity detector have consistently shown that when flow reversal normally occurs it begins during the latter part of systole when forward flow is beginning to decelerate (Fig. 9). This means that flow is moving in both directions simultaneously. The possibility that flow reversal can occur at the wall while there is still a net forward flow has been shown by Lang[4] and suggested by Streeter and associates. Streeter and co-workers speculated that when the pressure gradient reverses, the greatest effects will be on the slower moving fluid near the wall. The momentum of these layers decreases more rapidly than in the central flow stream which leads to flow reversal near the wall,

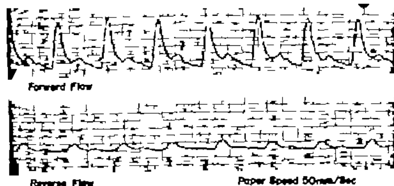


Fig. 9. Flow reversal (common femoral artery) in the normal subject begins when the velocity of the forward flow component is beginning to decrease.

even though the average velocity over the cross section does not reverse.

The pattern of flow reversal in the brachial and femoral arteries of the three patients with aortic insufficiency is difficult to explain. There appears to be three phases of apparent flow reversal that occur at the onset of systole, early diastole, and late diastole. The change on the reverse flow channel that occurs immediately after the onset of systole may represent wall displacement. While this motion is more evident on the reverse flow channel, there is a slight notch on the ascending limb of the forward flow component. Since the walls of the artery in the path of the sound beam are moving in opposite directions, the velocity of the wall should be detectable on both channels. The second component of flow reversal occurs during the deceleration phase of forward flow. Flow reversal normally occurs at this time. The third phase of reverse flow is in the latter part of diastole. We have not seen flow reversal in the normal subject at this time in the pulse cycle.

The changes in the femoral vein velocity pattern in patients with heart disease are of considerable interest. The observation that flow reversal occurs with tricuspid insufficiency would appear to have a straightforward explanation. In patients without tricuspid insufficiency and flow reversal associated with events in the cardiac cycle, a different explanation is required. It is likely that with congestive heart failure and an elevated venous pressure the major veins are distended at all times during the cardiac cycle. The chronic venous distention would provide better coupling so that both the pulsatile pressure and flow events could be detected as far peripherally as the femoral vein.

In the normal subject there is undoubtedly nearly total collapse of the major abdominal veins during the inspiratory phase of the respiratory cycle. When this occurs it would tend to damp out any disturbances in pressure and flow that are secondary to events on the right side of the heart.

The fact that the flow reversal in the femoral vein can and does change to a normal pattern is evident from the studies in the patient illustrated in Fig. 7. Two weeks after repair of an incompetent mitral valve, there was no reversal of flow in the femoral vein, with the forward flow component varying only with the respiratory cycle.

Determining absolute zero flow does not appear to be a serious problem with the directional velocity detector. Zero flow can be determined simply by moving the transducer off the vessel being studied.

These preliminary studies represent only the first step in application to a wide variety of disease states. The data, however, are of sufficient interest to indicate the direction that future efforts should take. Our studies indicate that directional information may be of value in the evaluation of (1) the normal physiology of arterial and venous circulation, (2) aortic valve disease, (3) arteriovenous fistulas, (4) extracranial arterial occlusive disease, (5) the venous flow patterns in patients in congestive heart failure, (6) the diagnosis of tri-

cuspid insufficiency and (7) the evaluation of venous flow patterns in patients with the postphlebitic syndrome

Summary

The application of a new transcutaneous directional ultrasonic velocity detector has been described This new device permits the simultaneous recording of forward and reverse flow in the arterial and venous system at any level through the intact skin The potential for this instrument in clinical research has been described

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Vectorcardiographic analysis of T wave inversion in the right precordial leads

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Inversion of the T wave in the right precordial leads in the absence of other changes in the adult electrocardiogram (ECG) is often difficult to interpret. It is observed in normal individuals but may also be present in patients with right heart strain, myocardial ischemia, or other pathologic entities. The purpose of this study is to assess the usefulness of the vectorcardiogram in determining the normality of such a finding.

Material and methods

The ECG's of 2,500 consecutive subjects, who have had vectorcardiograms recorded at the Cincinnati General Hospital, were reviewed. The subjects included members of the local police and fire departments and hospital personnel referred for routine examinations, as well as patients from the hospital wards and outpatient clinics. Individuals below the age of 16 were excluded. Standard 12-lead scalar ECG's were taken with a direct writing recorder and the corresponding vectorcardiograms were recorded immediately thereafter with either Sanborn or Hart vectorcardiographic equipment.* The Frank lead system[1] was used. The chest electrodes were placed at the level of the intersection of the fifth intercostal space with the sternum and the recordings were made with the patients in the supine position.

Individuals whose ECG's met the following conditions were selected for study: (1) The T wave was inverted in Lead V_1 or Leads V and V_2 or Leads V, V, and V_3. When more than one lead was involved, the magnitude of the inverted T wave should be greatest in Lead V. (2) The S-T segment and T waves were within the normal limits in the other leads. (3) The QRS complexes were normal in configuration and duration.

A total of 126 subjects met the above requirements. Sixty-nine were female, and 57 male. There were 69 Caucasians, 55 Negroes, and 2 Orientals. Their scalar ECG's were examined as to the depth and extent of the T wave inversion in the right precordial leads and to ascertain if the inverted T wave was symmetrical. If a diphasic T wave was present between the leads with inverted and upright T waves, a note was made as to whether it was of the positive-negative or negative-positive con

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*Sanborn Amplifier Model 65 and Viso-Scope Model 569A. Hart Electronics Model PV-3.

Table I Age distribution (126 subjects)

Age (yr)	16–19	20–29	30–39	40–49	50–59	60–69	70–79
No. of cases	4	36	1	29	25	8	1

figuration S-T segment displacement in the right precordial leads if present was quantitated

Since the precordial leads of the scalar ECG have their counterpart in the transverse plane of the vectorcardiogram analysis of the T loop was limited to the transverse plane The latter projection was viewed from above with the left end of the x axis designated as 0 degrees and the right end as ±180 degrees. The angles written in the clockwise direction from 0 degrees were considered as positive and in the counterclockwise direction as negative The direction and magnitude of the maximum T vector the length to width ratio of the T loop and the direction of inscription of the T loop were determined as well as the presence or absence of the normal slow inscription of the initial portion of the loop

The medical records of the 126 cases were reviewed with regard to their cardiovascular status and possible causes of T wave abnormalities A complete history physical examination and routine x-ray of the chest were available in all subjects.

Results

The age distribution and the clinical diagnosis of the 126 cases are listed in Tables I and II Seventy-four subjects had no clinical evidence of heart disease Their average age was 40 7 years Clinical evidence of heart disease was present in 52 patients and their average age was 37 7 The latter included four patients in whom the presence of organic heart disease was questionable.

T wave inversion was confined to Lead V_1 in 109 cases. The depth of the inverted T wave varied from 0 5 to 3 mm with a mean value of 1 1 mm Eleven patients had T wave inversion in both Leads V_1 and V_2 The depth of the inverted T wave

Table II Clinical diagnosis in 126 subjects with T-wave inversion in the right precordial leads

Type of heart disease	No. of cases
No heart disease	74
Rheumatic heart disease	16
Pulmonary embolism	7
Pulmonary stenosis	1
Pulmonary insufficiency	1
Chronic obstructive pulmonary disease	1
Atrial septal defect	1
Hypertensive heart disease	5
Patent ductus arteriosus	1
Systemic lupus erythematosus	1
Coronary artery disease	8
Primary myocardial disease and myocarditis	4
Pericarditis	1
Heart disease of unknown etiology	1
Questionable heart disease	4
Total	52

in Lead V_2 in this group varied from 0.5 to 3 mm with a mean value of 1 7 mm. Six patients had T wave inversion in Leads V_1, V_2 and V_3. The magnitude of the inverted T wave in Lead V_3 varied from 1 to 2 mm with an average value of 1 6 mm The S-T segment was isoelectric in 95 subjects. None of the rest had S-T displacement greater than 1 mm

The direction of the maximum T vector in the transverse plane in relation to the extent of the T wave inversion is shown in Table III Although the average direction of the maximum T vector became progressively more posterior as the number of leads with T wave inversion increased, the degree of posterior orientation varied considerably This was true regardless of whether or not clinical evidence of heart disease was present. In the 52 cases with heart disease the direction of the T vector

Table III Direction of maximum T vector in the transverse plane

Extent of T-wave inversion	No. of cases	Direction of maximum T vector		No. of patients without heart disease	No. of patients with heart disease
		Range	Mean		
V only	109	−50° t 44	10°	65	44
V and V	11	−25° t 46	5°	5	6
V V and V	6	−50° t −5°	−30°	4	2
Total	126			74	52

Table IV Correlation of the magnitude of the maximum T vector with the presence or absence of heart disease

Magnitude of maximum T vector	Total No. of patients	Patients without heart disease	Patients with heart disease
≥ 0.25 mv	90	65	25
< 0.25 mv	36	9	27
Total	126	74	52

Table V Clinical diagnosis in patients with uniform speed of inscription of T loop (6 cases)

Type of heart disease	No. of patients
Rheumatic heart disease with mitral stenosis	2
Pulmonary stenosis	1
Pulmonary embolism	1
Coronary artery disease	1
V heart disease	1

varied from −40 to 44 degrees with an average value of 3 4 degrees. In the 74 patients without heart disease it varied from −50 to 46 degrees with a mean of 8 6 degrees.

Table IV shows the correlation between the magnitude of the maximum T vector and the presence or absence of heart disease. In 36 patients the magnitude of the vector was less than 0 25 mv which was considered as the lower limit of normal as determined previously by the authors. Abnormally small T vectors occurred in 27 patients with heart disease and in 9 without.

The T wave was symmetrically inverted in the right precordial leads in 24 cases. Nine were found to have heart disease and 15 were normal. In the vectorcardiograms of these 24 cases the T loop was inscribed at a uniform speed in only one case. On the other hand loss of the normal initial slow inscription of the T loop was observed in 6 patients. Five of the 6 cases had clinical evidence of heart disease. The etiology of the heart disease varied (Table V)

Counterclockwise inscription of the transverse plane T loop was observed in 59 individuals and clockwise inscription was observed in 18 (Table VI) The T loop was considered to be narrow when the length to width ratio was 10 or greater Direction of inscription was disregarded in this group because of the frequent change from a clockwise to a counterclockwise loop or vice versa, when the loop is narrow A narrow loop as defined was found in 49 cases.

The clinical diagnosis of the 18 patients with abnormal clockwise inscription of the T loop is listed in Table VII There were only two cases without clinical evidence of heart disease One of them had severe anemia with a hematocrit reading of 17 per cent Her subsequent ECG s showed serial T wave changes which confirmed the abnormal nature of the T wave inversion Therefore in only one of the 18 patients with a clockwise T loop the abnormality of the repolarization process

Table VI. Direction of T-loop inscription in the transverse plane in relation to presence or absence of heart disease

Direction	Total No. of patients	Patients without heart disease	Patients with heart disease
Counterclockwise	59	42	17
Clockwise	18	2	16
Narrow			
L/W ≥ 10	49	30	19
Total	126	74	52

Table VII. Clinical diagnosis in patients with clockwise inscription of the transverse plane T loop

Type of heart disease	No. of patients
Rheumatic heart disease	
Mitral stenosis	3
Mitral stenosis and insufficiency aortic insufficiency	1
Mitral insufficiency	2
Pulmonary stenosis	1
Pulmonary embolism	1
Coronary artery disease	3
Ventricular septal defect	1
Primary myocardial disease and myocarditis	2
Heart disease of undetermined etiology	1
Questionable heart disease	1
Severe anemia	1
No heart disease	1
Total	18

*Serial T-wave changes observed

could not be explained on a clinical basis. The total number of patients having either a clockwise or uniformly inscribed T loop or both was 20. Eighteen had clinical evidence of heart disease and represented 35 per cent of this group of patients.

Although this study included only subjects with normal QRS complexes in the conventional ECG, the QRS loop was abnormal in the vectorcardiogram in 27 of the 126 cases. The changes were suggestive of myocardial infarction in 13 patients, right ventricular hypertrophy in 7, and were nonspecific in the remaining 7. Sixty-three per cent of the 27 patients had clinical evidence of heart disease while its incidence in patients with normal QRS loop was 35 per cent. An abnormal QRS loop was observed as frequently in patients with a T vector of normal magnitude as in those whose T vector was small (21 versus 22 per cent). However, vectorcardiographic QRS abnormality occurred relatively more often in patients with a clockwise T loop (7 of 18 or 39 per cent) than in those with a counterclockwise or linear T loop (20 of 108 or 19 per cent) and in patients with a uniform speed of inscription of the T loop (3 of 6 or 50 per cent) than in those with a normal speed of inscription (20 of 108 or 19 per cent). In six of the seven patients with a clockwise T loop the QRS changes were consistent with right ventricular hypertrophy.

Discussion

The T wave in the right precordial leads is normally inverted in the ECG of healthy infants and children. Such T wave inversion occasionally may be observed in the mid precordial leads including Lead V_4. With advancing age, the extent of T wave inversion decreases progressively so that in adults, it is usually limited to Lead V_1 and the majority have an upright T wave in all of the precordial leads.[4] However, the T wave is occasionally inverted in both Leads V_1 and V_2 or even V_3 in healthy adults; such a finding has been described as the persistent juvenile pattern.[4] This pattern has been observed more often in women than in men. Its relative prevalence in the Negro and Caucasian races has been a subject of controversy.[4]

During the routine interpretation of the scalar ECG, the normality of the inverted T waves in the right precordium up to Lead V_3 is often difficult to determine. This is especially true in the absence of QRS abnormality. Such pathologic entities as acute right heart strain from pulmonary embolism, early right ventricular hypertrophy, myocardial ischemia involving the anteroseptal region, and abnormality in the repolarization process due to other causes may result in T wave inversion limited to the right precordium. Serial ECG's are usually necessary to determine

the significance of such a finding but are not always available.

The extent of the T wave inversion in the right precordial leads can usually be related to the degree of posterior orientation of the T loop. When the entire T loop is more posterior than 25 degrees, the instantaneous T vectors will project on the negative side of the lead axis of Lead V_1 and an inverted T wave is recorded in Lead V_1. Further posterior displacement of the T loop will result in additional T wave inversion in Leads V and V_3, and so on. However, in this study there were considerable variations in the direction of the T vector even though the number of the right precordial leads with inverted T waves was the same. Such a wide range was found in individuals with or without heart disease. Therefore, the direction of the maximum T vector alone was not useful in the recognition of abnormal T wave inversion.

Our data indicated that abnormally small T loops were, indeed, encountered more often in patients with heart disease. Fifty-two per cent (27 of 5) of the patients with heart disease had a maximum T vector of less than 0.25 mv. In contrast, 12 per cent (9 of 74) of the subjects without heart disease had such a finding. The usefulness of this criterion for the determination of normality is, however, somewhat limited because of the relatively large percentage of false positive diagnoses. Th value of 0.25 mv. used for the lower limit of the normal transverse plane maximum T vector represented the 2.5 percentile value in 200 unselected normal subjects of various age groups. Its specificity does not, therefore, necessarily apply to the selected group of patients included in the present study.

The normal T loop is generally elliptical in shape. Its efferent limb is characteristically inscribed slower than the afferent limb. The absence of the initial slow inscription has been observed in association with myocardial ischemia. Our data further exemplifies the pathologic nature of this finding. In 5 of the 6 patients with this change definite clinical evidence of heart disease could be demonstrated. The finding was, however, nonspecific and was present in conditions other than myocardial ischemia. Since the slowly inscribed efferent limb of the T loop is related to the gradual slope of the early portion of the T wave in the scalar ECG, a symmetrical T wave may, therefore, be expected when the T loop is inscribed at a uniform speed. Such a relationship indeed often exists. However, the correlation as indicated in our study was rather poor. In only one of the 6 cases with uniform inscription of the T loop was a symmetrical T wave observed. The explanation is that the symmetry of the T wave depends not only on the uniform speed of inscription of the two limbs of the T loop but also on the relationship of each limb to the lead axis in question. A significant difference in the configuration of the two limbs, as well as in the angles that their corresponding component vectors subtend with the lead axis, will result in noticeable variations in their projection on the lead, i.e., the scalar T wave. For the same reason, a symmetrical T wave may be seen in the absence of a uniformly described T loop.

The normal T loop in the transverse plane is inscribed counterclockwise except when it is narrow. The most significant finding in this study was the presence of a clearly clockwise T loop in 18 cases. It occurred in 31 per cent (16 of 52) of the patients with heart disease and in only 3 per cent (2 of 74) of the subjects without heart disease. In one of the two subjects in the latter group, there was adequate evidence to suggest the presence of an abnormal repolarization process. The majority of the patients with a clockwise T loop were found to have diseases causing either pressure or volume overloading of the right ventricle or myocardial ischemia. The finding was, however, also found in other pathologic entities. The change was unlikely to be related to digitalis therapy since only five patients were receiving the drug. In a recent study concerning the effect of digitalis on the T loop, a reversal of the direction of T loop rotation was not demonstrated.

The direction of inscription of the T loop in the vectorcardiogram is often difficult to predict from the T wave in the scalar lead. This is possible if the T loop is oriented approximately perpendicular to a scalar lead with part of the loop on the

positive and the other part on the negative side of its lead axis. Under such circumstances a diphasic T wave will be seen and its configuration will depend on the rotation of the loop. For example, if the transverse plane T loop is directed at 0 degrees and the rotation of the loop is counterclockwise, the efferent limb will be on the positive side and the afferent limb on the negative side of the lead axis of Lead V₁. Therefore, a positive-negative type of diphasic T wave will be recorded in this lead. If the T loop is clockwise, the reverse will be true and a negative-positive T wave will be observed. Since a definite clockwise T loop in the transverse plane represents an abnormal T loop, the presence of a negative-positive type of diphasic T wave in the right precordial leads of the scalar ECG can be considered as pathologic. The application of this principle is, however, rather disappointing in the present study. Only two of the 18 cases with a clockwise T loop exhibited a negative-positive T wave in the right precordial leads. One of the explanations is the rather small amplitude of the inverted T waves in the right precordium in the cases studied. The transition from a negative to a positive deflection as the electrode was moved toward the left usually was represented by a small and rather flat T wave and the diphasic nature of the T wave may be difficult to ascertain. Another possibility is that the T loop may not be perpendicular to any lead. The entire loop is either on the positive or the negative side of the lead axis. Additional leads may be necessary to record the transitional diphasic T wave.

The significant number of patients with an abnormal QRS loop is of interest since the study included only subjects with normal QRS complexes in their scalar ECG. A detailed discussion of the discrepancy is beyond the scope of this communication but it is probably due to the higher sensitivity of the vectorcardiogram. The fact that patients with a clockwise or a uniformly inscribed T loop were more frequently associated with an abnormal QRS loop further suggests that the pathologic nature of these T loop changes may serve as additional evidence for the presence of heart disease.

From the data presented it is apparent that in patients with T wave inversion limited to the right precordial leads, vectorcardiographic demonstration of a uniformly inscribed or a clockwise transverse plane T loop is highly suggestive of the existence of heart disease. These signs were present in 35 per cent of the patients with heart disease included in this study but they did not suggest a specific pathologic entity.

Summary

The transverse plane T loop of 126 subjects with normal QRS complexes and inverted T waves in the right precordial leads were studied and correlated with their clinical diagnoses. The vectorcardiographic analysis included the determination of the direction and magnitude of the maximum T vector, the uniformity of the speed of inscription, and the direction of inscription of the loop. A clockwise and/or a uniformly inscribed T loop were found almost exclusively in patients with clinical evidence of heart disease. It is concluded that the vectorcardiogram may offer additional information permitting separation of patients with or without heart disease whose scalar ECGs show T wave inversion in the right precordial leads.

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Case reports

Convulsive syncope resulting from arrhythmia in a case of congenital deafness with ECG abnormalities

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In 1957 Jervell and Lange-Nielsen described a rare syndrome characterized by congenital bilateral deafness, attacks of unconsciousness, and prolongation of the Q-T time in the electrocardiogram (ECG). We consider it useful to describe a female patient who showed the characteristics of this syndrome. The attacks of unconsciousness in this case proved to result from cardiac arrhythmia.

Case report

History. The patient was an 8-year-old girl with deafness since infancy which necessitated the use of a hearing aid. Diabetes insipidus had become manifest at the second year of life. When the child was about 30 months old she had suffered syncope characterized by acute pallor followed by convulsion. The face demonstrated flushing after this attack. The attack had since recurred several times at varying intervals and the frequency had increased in the sixth year of life. The intensity of the attacks varied from something resembling a momentary lapse to attacks of the grand mal type with generalized clonic contractions. Neurological examination had never disclosed unmistakable abnormalities. Administration of phenobarbital, trimethadione, and amphetamine resulted in temporary improvement.

The frequency of the attacks increased again in the eighth year of life and the patient was admitted to an epileptic center for further examination. While an electroencephalogram (EEG) was being recorded the patient had an attack, and the pulse became irregular. A simultaneously recorded ECG showed the characteristics of ventricular tachycardia, turning into ventricular fibrillation. In view of these findings the patient was transferred to our hospital for further observation.

Examination. The patient was a girl who showed retardation of growth (height, 119 centimeters; weight, 24.4 kilograms). She suffered from bilateral deafness and used a hearing aid; her speech was normal. The pulse was irregular. The blood pressure, as measured in the upper arm, was 110/80 mm. Hg. There were no symptoms suggestive of heart failure. A soft systolic murmur was heard over the heart. The heart sounds were normal. This examination revealed no further abnormalities.

Laboratory data. Urine tests for protein, glucose, urobilin, and bilirubin yielded negative results. There were no abnormalities in the sediment, and no ammoaciduria. There was polyuria (2 to 5 L. per 24 hrs.); the specific gravity was 1.005 Gm. per milliliter. The pattern of diuresis did not change following administration of pitressin. The creatinine clearance was 30 ml. per minute. Blood tests yielded the following results: hemoglobin, 12.3 Gm. per 100 ml.; leukocyte count, 8,500 per cubic millimeter with normal differential count; erythrocyte sedimentation rate, 9 mm. after one hour; urea, 0.49 Gm. per liter; creatinine, 9 mg. per liter; calcium, 5 mEq. per liter; phosphorus, 51 mg. per liter; electrolytes, normal; glucose tolerance test, normal; bilirubin, 3 mg. per liter; alkaline phosphatase, 297 millimoles per minute per liter; thymol turbidity, 0.35 U.

From the [illegible] Hospital, Utrecht, The Netherlands.
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**From the Department of Internal Medicine (Heads: Prof. Dr. L. J. Jordan and Prof. Dr. L. A. [illegible]).
***From the Intensive Care Unit.

transaminase activity normal protein pattern un disturbed cholesterol 2 48 Gm. per liter uric acid 74 mg per liter a antistreptolysin titer normal toxoplasma tests negat e lupu erythematosus test, negative rheumatoid arthritis tests, normal syphilis serology negative Arterial blood g nalys is produced normal lues

Electrocardiogram There w sinus rhythm with some sinus arrhythmia nd ma y m ltifocal ventricular extrasystoles. The Q-T time was unequivocally prolonged 0 62 sec t heart rate of 56 per minute I the precordial lead from V1 through V the T deflection was neg tiv (Fig 1)

Phonocardiogram A ormal fir t sound wa followed by a fusiform murmur ma nly of medium frequency and ending prior t the inconstantly split second sound A low t medium frequency atrial sound w observed over the pex The arterial and venou pulse nd pex t ing were normal.

Radiograph A best y h owed no pulmonary abnorm l ties The he rt shadow wa not enlarged.

Otological examination Bilateral perceptive deafness (verage 60 db) was found.

Ophthalmological examination No abnormalities were found.

Family study The patient was from a family with four hildren, all in good health. There as no consanguinity and no history of particular disease, especially no deafness or convulsions The ECG was found normal in all these individuals, as cre the creati ine and uric acid values in the blood.

Observation report and s pplemental studies At tacks were observed from the first day after the child admis ion. At the onset of an attack the girl began to cry and a brief syncopal attack was followed after a few seconds. At that moment the face was pale. In more protracted attacks convulsions occurred sometimes with urinary incontinence. A consciousness returned, the face briefly assumed bright red color The pulse was rapid at the onset of the ttack nd subsequently was no longer perceptible

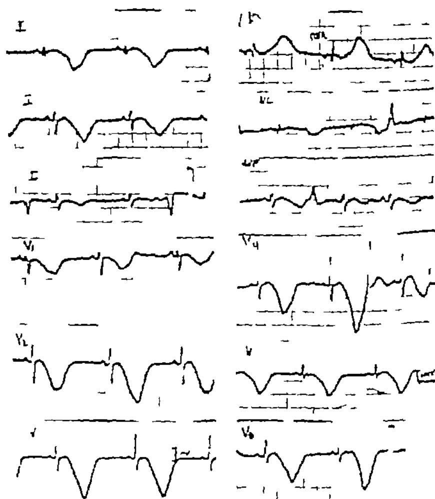


Fig 1 ECG after admission. Sinus hythm with ery long Q-T time and broad negative T waves in the standard leads AVL and the precordial unipolar leads. A few supraventricular extrasystoles in Lead III show aberrant conduction.

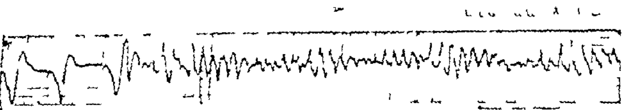


Fig 2 ECG during syncope. Sinus rhythm and ventricular fibrillation after ventricular extrasystole.

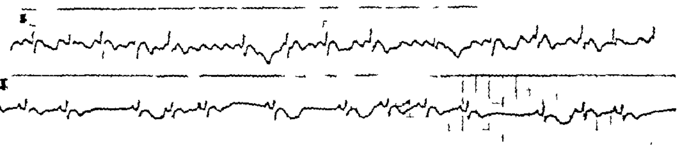


Fig 3 (Top) Atrial flutter with varying A V block and normal intraventricular conduction (top curve) sinus rhythm with pronounced sinus arrhythmia. (Bottom) ECG during syncope. Sinus rhythm and ventricular fibrillation after a ventricular extrasystole.

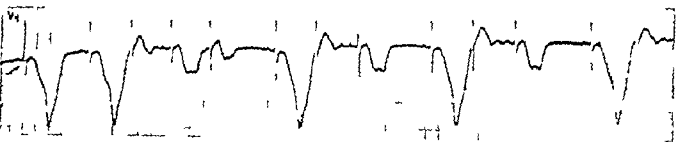


Fig 4 ECG. Sinus rhythm with pronounced sinus arrhythmia varying width shape and amplitude of T waves.

An ECG recorded during an attack disclosed the features of ventricular tachycardia with course ventricular fibrillation (Fig. 2). As a rule the ECG showed but rare features with multiple ventricular extrasystoles originating from several foci. Moreover, tachycardia existed following attacks. In general there was sinus rhythm with normal AV conduction, but on two occasions an atrial flutter (330 per minute) with varying AV block was recorded (Fig. 3). A pronounced sinus arrhythmia sometimes occurred (Fig. 3, bottom row). The depth and shape of the T waves varied greatly, not only at different times but also during a single recording. There seemed to be some correlation with the length of the preceding diastole (Fig. 4). In the precordial lead the T waves were usually large, pointed, and negative.

In view of the nature of the ECG changes with predominance of heterotopic impulse formation, the child was treated with quinidine sulfate and Mararex. On the third and fourth day of this medication very frequent attacks with the mentioned arrhythmia occurred for hours. After discontinuation of the quinidine, the attacks diminished.

Administration of digitalis, prednisone, adenosine triphosphate, insulin with additional glucose administration, and phenobarbital never had any distinct effect.

Further studies had meanwhile revealed that the polyuria had to be of renal origin, in view of the disturbed ... following fluid restriction and the negative result of pitressin administration. The nature of the renal disorder was not established. The creatinine clearance of 30 ml. per minute indicated distinct renal insufficiency. Because of the arrhythmia only superficial investigation could be done.

Biochemical studies revealed marked hyperuricemia, which of course may have resulted from the disturbed renal function. There was no family history of gout. The possibility of primary gout, however, could not be ruled out. Gout is known to be associated sometimes with cardiac disorders, and hyperuricemia has been described in patients with perceptive deafness. Since no treatment so far instituted had been efficacious, we decided to start Benemid medication in increasing doses up to 250 mg. 3 times a day, combined with sodium bicarbonate. This medication was continued for about two months. The attacks rapidly diminished in frequency and ultimately disappeared completely. Hearing showed distinct subjective improvement. The patient no longer used her hearing aid. The polyuria gradually diminished from an average 3.5 to 2.5 L. per 24 hours and renal function seemed slightly improved after two months when the clearance was 47 ml. per minute. The blood uric values were normalized (Fig. 5). The urinary uric acid excretion averaged 310 mg. per 24 hours before institution of treatment. On the third day of treatment the excretion was measured as 1976 mg. per 24 hours. The subsequent urinary excretion averaged 600 mg. per 24 hours.

After two months' treatment the unfortunate decision was made to reduce the Benemid dosage to 250 mg. once a day. The child suffered a fatal attack on the eighth day. The ECG features were those of

mg%
10
5
before
after

Fig. 5. Blood uric acid values before and after start of Benemid medication.

ventricular fibrillation. Immediate attempts at resuscitation with electrical defibrillation failed.

Postmortem findings. The heart weighed 115 grams. Both ventricles were slightly dilated. The foramen ovale was closed. The endocardium showed no swelling. Valves and cords appeared to be normal. No focal abnormalities were found in the myocardium. The left kidney weighed 33 grams and the right weighed 85 grams.

Microscopic examination disclosed normal features of myocardial tissue. The renal sections showed considerable autolysis. Some Bowman capsules were swollen. No other abnormalities were observed.

Discussion

In 1949 Levine and Woodworth[4] examined an 8-year-old male deaf-mute suffering from attacks of unconsciousness. The ECG showed conspicuous prolongation of the Q-T time and varying aberrant shapes of the T waves. Sudden death occurred at age 13.

In 1957 Jervell and Lange-Nielsen[1] described a Norwegian family in which four of the six children suffered from congenital

bilateral deafness and syncopal attacks in which the ECG showed a prolonged Q-T time. Three of these children died.

An ECG study among children with bilateral perceptive deafness in English and Irish institutions made by Fraser and associates[7, 8] disclosed nine cases with significantly prolonged Q-T times. Eight of them had a history of syncopes. An attack was observed in two children, in one of whom the pulse could not be felt during a full minute.

More patients with this syndrome have since been described[9-13] bringing the total number of known cases to 18.

Recently, moreover, there have been reports[14] on patients with syncopes whose ECG's showed the characteristic Q-T prolongation and T changes although they had normal hearing. It is of interest that an ECG recorded during an attack showed ventricular fibrillation in two of these cases. Ventricular extrasystoles were observed in another child.

In our patient, the syncopes which had the clinical characteristics of Stokes-Adams attacks were caused by ventricular flutter and ventricular fibrillation. Between attacks, moreover, there were ventricular extrasystoles and supraventricular arrhythmic disturbances which had not been previously observed in patients with this syndrome.

We consider it plausible that the syncopes reported in the literature were based on a similar mechanism. In view of the close similarities of ECG changes between our case and those described by Romano, Ward, and Barlow, it is attractive to suppose that their cases, too, were instances of the syndrome described by Jervell and Lange Nielsen. Thus the cardiac anomaly would not per se be linked with the hearing disorders, which may imply that all these cases are based on the same genotypical abnormality but with varying forms of expression. The remarkable fact remains that no arrhythmia has so far been observed in the cases with deafness.

The significance of the hyperuricemia in our patient and the protracted clinical improvement during Benemid medication is not easily established because the observations concern only a single patient. Other authors, however, obtained normal blood uric acid values in two cases. Nevertheless, the hyperuricemia might have a central position in the syndrome described.

Summary

A description is given of an 8-year-old girl with the syndrome of Jervell and Lange Nielsen consisting of congenital deafness, prolonged Q-T time in the ECG, and attacks of unconsciousness. In addition there were extrasystoles, ventricular tachycardia, ventricular fibrillation, and atrial flutter.

The syncopes proved to be based on circulatory insufficiency as a result of ventricular fibrillation.

The child suffered in addition from diabetes insipidus on the basis of a disturbance in renal function, and hyperuricemia was repeatedly found. The girl died as a result of an attack of ventricular fibrillation after an initial period of considerable clinical improvement upon Benemid medication.

It is suggested that the recently described combination of Q-T prolongation in the ECG and syncopal attacks as a result of ventricular fibrillation must be regarded as the same genotypical entity. The possibility is mentioned that this case may have presented a symptom complex in association with hyperuricemia.

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Calcinosis of the arteries with coronary calcification in infancy

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About sixty cases of calcinosis of the arteries with coronary calcification in infancy have been published in the literature. The disease was first described by Bryant and White[1] in 1901 An earlier report of generalized arterial calcinosis in infancy by Durante[2] in 1899 did not mention any coronary involvement.

There are almost as many case reports about this disease as there are children with the disease. Some of these reports are review articles. [7] However due to the early death of these infants, only a few electrocardiograms of this disease are available. [12] Aortograms demonstrating coronary occlusion in these infants have not been published The vast majority of the cases were not diagnosed during life. Therefore, most articles concentrate on the pathologic and histologic findings. Only a few of the patients reported upon were still alive at the end of the first year The patient to be described here was diagnosed by conventional roentgenograms demonstrating peripheral arterial calcinosis at the age of six months. When he was seven months old an aortogram showed coronary involvement. He then was followed until his death at the age of one year and four months

Vitamin D hypersensitivity has been discussed as a possible etiologic factor in most articles about this disease A vitamin D loading test was carried out in the patient. Since he is one of the oldest patients observed and because of the extensive diagnostic workup, the publication of this case is justified. It is not the purpose of this communication to review the literature.

Case report

This boy was born on Dec. 5, 1965 His birth weight was 3 500 grams His length was 51 centimeter When he was four months old, the mother noted for the first time that he was dyspneic and tachypneic At the age of five months, he developed pneumonia and was hospitalized with St Bernward Hospital, Hildesheim. At the time of admission he displayed cardiac failure The heart was markedly enlarged. There was a Grade II systolic murmur along the left sternal border loudest in the third left intercostal space. The electrocardiogram (ECG)

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showed right ventricula hypertrophy Labor tory dat were normal. Blood calci m w 8 8 mg per cent cholesterol was 169 mg per cent A congenital cardiac defect was spected

H cond tion mproved follow ng tre tment of the pneumonia He w dig t lized There as the general impres ion th t the boy had pain his legs. Roe tgenogr ms of the extrem ties showed ext sive c lcinosis of the peripher l arteries (Figs 1 nd 2).

At the age of seven month he w eferred t the Department of Pediat Card logy of the U i ersity of Götti gen f r f rther ardiac tudies The cardiac enlargement d the rdiac m rm had not changed The ECG showed an is of + 100° There was some right ventricular hypertrophy nd left vent ic lar h pertroph w th t m There were deep Q es V nd V Fig 3 show the ECG

Right heart theterization w arried out. There ere normal ox ge sat trons i the right heart nd the pulmonary artery The pressure the right ventricle 55 per 0 mm Hg nd the pulmonary rtery t 52 per 20 mm Hg Selec t ve ngiocard g ph w th jection of ont t medium int th ma pulmonary rtery howed pulmonary rteries w th narrow l men nd rigid ppe ance (Fig 4) There were some pot i the peripher l pulmonary rteries uggesting calci- fication

I second session, retrogr de left entricula theterization w carried out The pressure the left ventricle 105 per 0 mm Hg nd in the scending aorta t w 105 pe 60 mm Hg The ox ge sat rat on i the orta w 95 0 per cent R trograde ortogr phy showed coronary occl ion particularly of th circumflex br nch of the left cor ary artery The right coronary rtery was f lled t ll (Fig 5 nd 6).

A vitami D load ng test for the determination of serum vitam D activity before nd after loading was rried out Vit mi D ctivity was determined according to the method f V tener Following a diet free of v tamin D control blood samples were taken Then the patient received 500 units of vitamin D per day for fou days. T enty fou hour after the last doses of vit m D blood samples ere t ken for the determination of D act ity The control sample had vitamin D activity of 170 nit per cent. Twenty-fou hours following loading



Fig 1 Roentgenogr m of both legs, showing calcification of distal arteries.

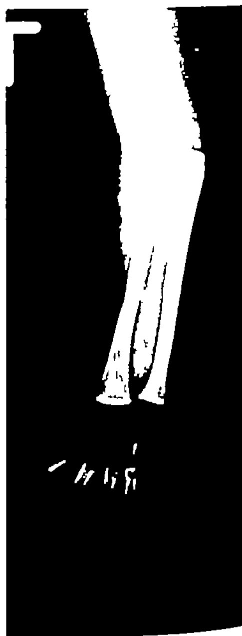


Fig 2 Roentgenogr m of left arm Calcification of distal arteries.

It was 150–170 unit per cent. These are normal values for this amount of loading. Control loading tests in normal subjects have been carried out. They showed similar values.

Coronary attacks were not observed when the patient was in the hospital. He was discharged at the age of eight months. In March of 1967 when he was one year and three months old he was hospitalized again at the hospital in Hildesheim because of pneumonia. Following improvement he was discharged from the hospital. Three days later on April 4, 1967 the boy was brought to the hospital by an ambulance. He was dead on admission. He had died within a half hour during a coronary attack.

At autopsy the diagnosis of generalized calcinosis of the arteries with coronary calcification was confirmed. There was predominant left ventricular hypertrophy and some right ventricular hypertrophy. Scars and infarctions could be seen in the wall of the left ventricle. Calcification was most pronounced in the wall of the smaller muscular arteries. It was very severe with many subtotal occlusions in both coronaries, the arteries of the extremities, and less severe in the branches of the pulmonary artery. Histologic examination showed thickening of the intima with spots of calcium and fragmentation of the internal elastic membrane. There were only a few calcified rests of this membrane in the coronary arteries. Figs. 7 and 8 are cross-sections of the coronaries. Fig. 7 shows subtotal coronary occlusion due to proliferation of the intima and complete interruption of the internal elastic membrane. Large calcium deposits can be seen in the left lower area. Fig. 8 shows marked thickening and vascularization of the intima and calcium deposits. The renal arteries were normal.

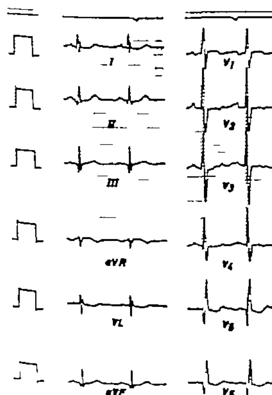


Fig. 3. Electrocardiogram. See text.

Discussion

Calcinosis of the arteries with coronary calcification in infancy is a very rare disease. It usually leads to early death in infancy. Calcinosis of the peripheral arteries of the extremities may be diagnosed on conventional roentgenograms as demonstrated here. Coronary occlusion has been shown in our patient by means of retrograde aortography. However, in most of the cases the disease progressed so rapidly that extensive cardiac studies were not done.

The ECG is not specific for this disease. It shows left, right, or biventricular hypertrophy, deep Q waves in V_5 and V_6, and myocardial strain. The ECG in the left precordial leads of our case is like that seen in many patients with the Bland-White-Garland syndrome. The changes in aVL, however, are different than is usually seen in the Bland-White-Garland syndrome in infancy. There is no reason to believe that it could not be similar to the ECG of that syndrome. The electrocardiographic pattern may depend upon the duration of the finally fatal disease.

Of special interest is the aortogram and the angiocardiogram of the pulmonary artery of our patient. The former shows definite coronary occlusion. However, if one did not know from roentgenograms of the extremities that the patient had calcinosis, it would be hard to say that this occlusion is caused by coronary calcification. On the other hand, to our knowledge similar coronary occlusion has not been demonstrated on angiography of any other known disease involving the coronary arteries of infants. If more coronary angiograms done in this disease become available, it may turn out that the angiographic appearance as shown in our case is characteristic of coronary calcification.

The interpretation of the angiocardiogram of the pulmonary artery is more difficult. Angiography shows the lumen of



Fig. 4. Angiocardiogram. Pulmonary artery with small lumen, calcium spot in the periphery. Rigidity.

a vessel and does not say much about the wall of the vessel. However, structural changes of the wall can alter the angiographic appearance of the lumen. In our case the pulmonary artery gives the appearance of a hypoplastic vessel with a small lumen. The narrow lumen and the rigidity of the pulmonary vascular tree comes close to the pathology of this vessel with calcified intimal proliferations.

Stryker[22] has pointed out that in contrast to Mönckeberg's medial arteriosclerosis, the calcification occurs in relation to the internal elastic membrane. In this area are the earliest deposits of calcium. As the calcium deposit increases, it encroaches on the media. In well-advanced cases, the internal elastic membrane is extensively fragmentated and in many areas it can no longer be recognized. In these cases, the process actually involves all three arterial coats. Coronary occlusion is due to extensive proliferation of the intima.

The etiology of the disease is unknown. Many causes have been suggested such as an alteration in calcium and phosphorus metabolism,[8] a congenitally defective elastic tissue in the arterial wall,[17] an injury of the intercellular substance of the media,[11] and an allergic process.[11] Zischka[1] saw eosinophilic leukocytes in the arterial wall. Excessive intake of vitamin D of the mothers during pregnancy, large amounts of vitamin D given to infants, or a hypersensitivity of vitamin D have been discussed as possible causes by many authors. We feel these causes can be justified because similar lesions can be produced in rats by excessive amounts of vitamin D. Our loading test with the determination of vitamin D activity in the serum of our patient seems to exclude this etiologic factor. However, calciphylactic arteriopathy has been produced by several authors[1, 21] according to the method of Selye. Seifert and Dreesbach[21] pointed out that the morphologic characteristics of calci

Fig. 5. Retrograde aortogram showing occlusion of left coronary artery. No filling of right coronary.



Fig. 6. Retrograde aortogram, lateral view. Occlusion of left coronary.

phylactic arteriopathy are compatible with the morphology of calcinosis of the arteries with coronary calcification in infancy.

The disease has been termed "idiopathic generalized arterial calcification" by Ivemark and co-workers, and "arteriopathia calcificans infantum" by Zischka. The latter term seems to be appropriate.

Summary

This article describes the case of an infant with calcinosis of the arteries with coronary calcification. The disease was diagnosed by conventional roentgenograms of the extremities at the age of five months. Coronary involvement was demonstrated on retrograde aortography at the age of seven months. Angiocardiography showed involvement of the pulmonary arteries. The patient lived to the age of one year and four months. A vitamin D loading test excluded vitamin D hypersensitivity. The histologic findings are in accordance



Fig 7 Cross-section left coronary artery Subtotal occlusion Intimal proliferation and complete interruption of internal elastic membrane. Calcium deposit (Elastic-van Gieson X65)



Fig 8 Coronary artery Thickening and vacuolization of the intima calcium deposit (Hematoxylin and eosin X132)

with other cases published in medical literature

Our sincerest thanks to Dr Ilse Antener of the Nestlé Company, Geneva, Switzerland for the determination of vitamin D activity in the blood serum of this patient

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QRS changes, pulmonary edema, and myocardial necrosis associated with subarachnoid hemorrhage

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Profound cardiovascular changes occur with severe head trauma, spontaneous intracranial hemorrhage, or thrombotic, ischemic stroke. Weisman[1] in 1939 documented pulmonary edema at autopsy in both spontaneous and traumatic intracerebral hemorrhage. Additional observers have confirmed these findings in both postmortem and clinical observations.[2-4] Laine and Smith and Richards reported a 46 per cent and 52 per cent incidence of pulmonary edema, respectively, in consecutive autopsy series of patients dying of intracranial disease.

Burch and associates[7] and Levine[8] associated ECG changes with intracerebral hemorrhage and stroke. Burch's group emphasized large T waves (both upright and inverted), large U waves, and prolonged Q-T interval, but others emphasized deep T wave inversion in the precordial leads in addition to the S-T changes, U waves, and prolonged Q-T interval.[6, 7] These symmetrical inverted T waves in precordial leads under other circumstances would be considered as evidence of myocardial ischemia or subendocardial infarction.

Changes in the initial vector of the QRS complex diagnostic of transmural infarction in association with acute intracranial disease have been rarely reported. Meyer reported a case in which Q waves in aVL developed, suggesting a lateral wall infarction with normal coronary arteries at autopsy. Pfister and de Pando[1] described an electrocardiogram (ECG) consistent with an acute anterior transmural myocardial infarction in such a patient with normal coronary arteries at postmortem examination.

In most of the cases of ECG changes associated with acute intracranial disease in whom postmortem studies were carried out, the heart is reported to be without evidence of recent infarction or myocardial necrosis.[9, 12, 13, 14, 15, 16, 18]

There are two reports of pathologic changes in the myocardium with anatomically normal coronary arteries in association with an acute intracranial lesion.[17, 18]

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[1-] and associates report three cases f intracranial hemorrhage who had T wave hanges, and at postmortem examination mall subendocardial hemorrhages were een Smith and Tomlinson[10] report 29 in tances of subendocardial hemorrhage in 35 autopsies in patients dying of intra ranial disease. In 607 additional autopsies f patients without neurologic disease only hree cases of subendocardial hemorrhage ere observed

The mechanism by which pulmonary dema and ECG changes occur in these pa ients has remained speculative.[7] [12]
The present report is an illustrative case vith subarachnoid hemorrhage pulmonary dema, and ECG changes of transmural nfarction in the presence of normal coro-ary arteries. The patient s clinical course and pathologic changes in the myocardium uggest mechanisms whereby the intra ranial insult caused the cardiovascular hanges.

Case history

D B (U iversity Hospital N 8-5-914-70), previously healthy 49-year-old Caucasian woman was admitted t the University Hospital on M y 9 1967 after suddenly collapsing while sitting On admission she was comatose, but he was able t move all four extremities. Her blood pressure of 270/140 mm. Hg dropped to 170/100 mm. Hg with hydralazine treatment. Her respirations were rapid she had bilateral Babinski' sign, stiff neck, eyes deviated t left, Isocoria with the left pupil larger than the right, a left retinal hemorrhage, and right hemiparesis. Admission chest film (Fig 1) showed the haracteristic picture of acute pulmonary edema. The admission ECG (Fig 2) showed S-T segment changes in V_{1-4} consistent with subendocardial ischemia. A lumbar puncture revealed grossly bloody cerebrospinal fluid with an opening pressure of 550 mm. saline, indicating subarach noid hemorrhage. Other routine laboratory studies were normal except for moderate hyperglycemia. The pulmonary edema resolved quickly with intubation nd tracheal suction.

By the following day she was responsive, but bilateral Babinski' sign and stiff neck still present. Cerebral angiography demonstrated aneurysms of the left anterior cerebral artery left middle cere bral artery and possible aneurysm t the bifur



Fig 1 Chest -ray taken on admission showing severe, acute pulmonary edema.

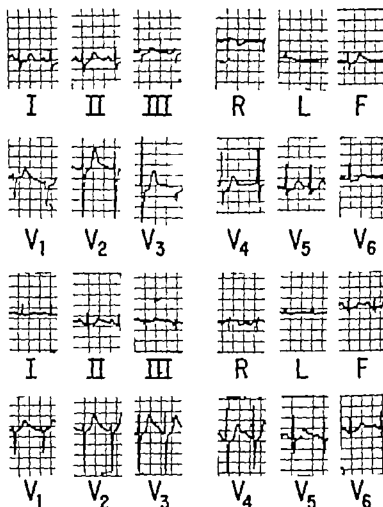


Fig. 2. *Top two rows:* ECG on admission showing S-T segment depression consistent with subendocardial ischemia. *Bottom two rows:* ECG two days later showing development of Q waves in II, III, and aVF.

cation of the basilar artery. An ECG dated May 11, 1967 showed development of Q waves in II, III, and aVF consistent with a diaphragmatic infarction (Fig. 2). On May 12, 1967 craniotomy was performed and the left anterior cerebral artery aneurysm was encased in methacrylate. During half of the six hour procedure the blood pressure was 80/50, but rhythm was stable and rate about 110.

After several days she became less responsive with increasing neck rigidity. Repeat lumbar puncture showed again bloody cerebrospinal fluid with an opening pressure of 430 mm. saline. Another ECG on May 17, 1967 (Fig. 3) showed larger Q waves in II, III, and aVF but no loss of R-wave progression in the anterior precordial leads, suggesting extension of the infarct. A final ECG on May 23, 1967 (Fig. 3) was essentially unchanged. At no time were the S-T segment elevation and T wave inversion usually associated with transmural infarct seen. Serum glutamic oxalacetic transaminase (SGOT) and serum lactic dehydrogenase (LDH) determinations obtained on May 13, 17, 18, 19, and 20, 1967 were normal.

On May 22, 1967 repeat subarachnoid hemorrhage occurred with rise in blood pressure to 230 mm. Hg systolic. She again had acute pulmonary edema which responded to intravenous ethacrynic acid. She went into a deep coma and died the following day of her intracerebral insult.

At no time did she receive any catecholamines or catecholamine-releasing drugs. She received hydralazine, quinidine prophylaxis, and Dilantin.

Autopsy findings

At autopsy the heart weighed 370 grams. The coronary arteries, which had a normal distribution, had only small, yellow, slightly raised intimal plaques which did not encroach upon the lumen of the vessels. The myocardium was homogeneously red-brown and did not show focal areas of discoloration, softening, hemorrhage, or fibrosis. Incubation of a coronal section of the heart with Nitro-Blue Tetrazolium to reveal enzymatic dehydrogenase activity demonstrated a normal uniform reaction without demonstrable lesions.

Microscopically, throughout the ventricle there were multiple foci of myocytolysis with loss of myo-

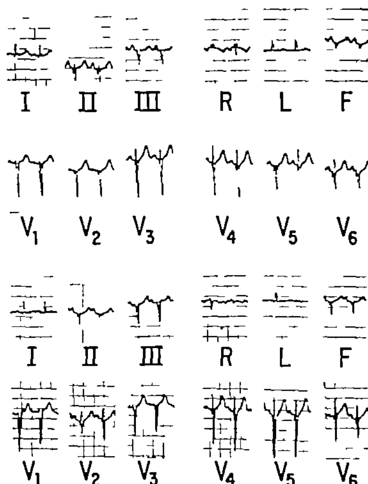


Fig 3 *Top two rows* Follow-up ECG showing progression of inferior Q waves and loss of precordial R wave progression (5/17/67). *Bottom two rows* ECG on day of death (5/23/67) Note lack of change

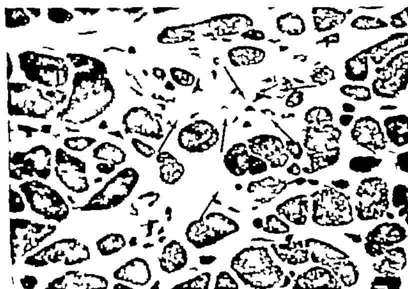


Fig 4 Cross-section of myocardium which shows loss of myocardial cells (arrows) with collapse of the supporting stroma containing myocardial cell debris and macrophages. (Gomori trichrome. ×450)

cardial cells, collapse of the supporting stroma, and few surrounding mononuclear cells frequently containing phagocytosed lipofuscin pigment (Fig. 4). These extensive small foci of evolving cell necrosis did not follow a vascular distribution and were surrounded by normal appearing myocardial cells which accounted for the inability to grossly detect this injury.

An aneurysm at the bifurcation of the basilar artery had bled into the third ventricle filling the entire ventricular system with clot. Microscopically the posterior hypothalamus showed neurons with varying degrees of pyknosis and chromatolysis.

The lungs showed minimal pulmonary congestion and edema, and there was hepatic congestion.

Discussion

Although pulmonary edema and electrocardiographic changes are associated with acute intracranial disease, the exact mechanisms by which they are associated remain unclear.

The neural pathways involved are most likely those of the sympathetic nervous system. Severe hypertension and tachycardia, which were seen in this case, are consistent with a massive sympathetic discharge. Multiple experiments indicate that the sympathetic nervous system is the mediator of pulmonary edema associated with intracranial disease. Von Frey[20] produced pulmonary edema by vagotomy. Luisada and Sarnoff[21] demonstrated a protective effect with sympathetic blocking agents, and a deleterious effect with atropine and epinephrine on pulmonary edema caused by rapidly injecting saline into the carotid arteries of dogs. Sarnoff and Sarnoff[22] demonstrated that vagotomy had no effect in dogs but spinal anesthesia gave a protective effect from pulmonary edema precipitated by intracisternal fibrin. Maire and Patton[23] found that cervical spinal cord transection in rats prevented pulmonary edema caused by lesions stereotactically placed in the preoptic nucleus of the hypothalamus where vagotomy had no effect. Finally, they showed that epinephrine produced pulmonary edema.[24] They concluded that the sympathetic nervous system was the neural pathway involved.

The neural pathway accounting for some of the ECG changes associated with intracranial disease is probably sympathetic. Porter and associates[25] were able to produce T wave inversion by stimulation in the central hippocampus of cats which could be blocked by transection of the cervical spinal cord.

In our patient the presence of tachycardia and severe hypertension requiring antihypertensive agents suggests a massive sympathetic discharge. In this case the diffuse myocardial necrosis following no vascular pattern is very similar to the focal myocardial necrosis of norepinephrine myocarditis described by Szakács and associates.[17-19] It is unlikely that mild hypotension during the craniotomy played a part in the myocardial changes, as ECG changes, including changes in Q waves, had occurred prior to this time (Fig. 2).

The etiology of the ECG changes and pulmonary edema would appear to be the same, i.e., direct myocardial damage. Pulmonary edema probably represents true left ventricular failure. The concept of simple fluid shift to the pulmonary circuit, which would cause pulmonary edema without any change in cardiac function, is not tenable. In the presence of a competent left ventricle, fluid shift to the pulmonary circuit would increase left ventricular filling pressure and then left ventricular output, leading to a new equilibrium. Accumulation of fluid in the pulmonary circuit leading to pulmonary edema implies relative left ventricular failure.[11] The mechanism by which left ventricular failure occurs is neurohumoral damage to myocardial cells. Whether this represents focal ischemia due to constriction of the myocardial microcirculation or a direct toxic effect of the catecholamine on the myocardial cell is unknown. In those patients who do not exhibit hypertension and other findings of diffuse sympathetic discharge, the catecholamine release may be localized in the myocardium.

Despite QRS changes showing extensive myocardial infarction in association with CNS disease, postmortem examination revealed normal coronary arteries. The spotty focal necrosis of myocardial cells would be more likely to produce the T wave changes of subendocardial ischemia or infarction without development of Q waves. This patient represents one extreme of the spectrum of this disease electrocardiographically: the very extensive myocardial necrosis seen pathologically correlates well. Sufficient myocardial necrosis to produce the electrical picture of a transmural in-

farct is rare. It is likely that some of the myocardial damage seen in these patients is reversible accounting in part for the previously reported normal pathologic studies. Finally, lesser degrees of this type of myocardial necrosis can be very subtle as fibrosis characteristically does not develop.

We postulate that acute intracranial disease stimulated sympathetic centers in the hypothalamus, which resulted in release of catecholamines within the myocardium and/or systemically. These agents are presumably in sufficient concentration at the myocardial cellular level to cause damage to the contractile apparatus and to the cell membrane, accounting for both the pulmonary edema and ECG changes.

The above mechanism can be tested by several means. Serial serum enzymes, especially LDH isoenzymes should be used. Urinary catecholamines could be measured. There should be more careful pathologic examination for the subtle changes described. Finally, staining the tissue for catecholamines would give useful information.

We would emphasize that the observed ECG changes do indicate myocardial disease. Although severe and prolonged heart failure and/or shock are rare, such patients with the more severe ECG changes should be treated as if myocardial infarction is present. Careful observation for arrhythmias is recommended. Finally, donation of a heart from a patient dying from acute cerebral disease may be inappropriate because of the risk of significant myocardial damage induced by neurohumoral mechanisms.

Summary

A 49-year-old Caucasian female without history of cardiovascular diseases presented with a subarachnoid hemorrhage, severe hypertension and pulmonary edema. Despite QRS changes of extensive myocardial infarction, postmortem examination revealed normal coronary arteries. Microscopic study showed extensive myocardial necrosis unrelated to vascular pattern and similar to that induced by exogenous catecholamines. The ECG changes and pulmonary edema appear to be the result of a neurohumoral myocarditis with left ventricular damage and failure. Implications for heart transplantation are cited.

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Renal countercurrent mechanisms
Structure and function

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Boilermakers have known and exploited the principle of countercurrent exchange since the early nineteenth century.[4, 75]

'The design is for the cold air to pass down from the top of the boiler (Fig. 1) to get heated in its passage and to pass up through the fire case in the hot state.' (From a letter written in 1830 by the Cornish engineer Trevithick.[75])

Some years later Claude Bernard suggested that an exchange of heat might also occur between arteries and veins in man. Other countercurrent mechanisms have since been identified in the swim bladder and gills of the fish and in the placenta, peripheral circulation, and renal medulla of the mammal.[1, 2, 28, 37, 38, 43, 76]

In principle a countercurrent system consists of two closely apposed parallel tubes through which solutions pass in opposite directions (Figs. 2, D and 3, A). Depending on the character of the separating wall, solvent, solute, or heat passes from one tube to the other and reverses its direction of flow. This basic process may be modified to produce equilibrating, separating, or multiplying effects. The purpose of this review is to consider first the nature of these three effects and second the extent to which each may contribute to the concentration of urine within the renal medulla of the mammal.

Equilibration by countercurrent exchange

Several factors influence the movement of solute and water through a permeable membrane: solute concentration gradients, permeability characteristics, active transport processes, and the pattern of flow on opposite sides of the membrane. The present discussion is concerned only with the effect of flow. Four differing patterns are illustrated in Fig. 2. If, for example, 0.2M and 0.6M solutions of sodium chloride reached equilibrium while flowing at the same rate through a concurrent system (Fig. 2, C), both would emerge at approximately 0.4M. If, on the other hand, the same original solutions were passed at the same rate but in an opposite direction through an identical system (Fig. 2, D), the 0.2M solution would be augmented to 0.6M and the 0.6M solution would be reduced to approximately 0.2M. This property of complete exchange is not shared by the other equilibrating systems illustrated in Fig. 2. The distinction is of both technical and biological interest. Countercurrent dialysis, for example, is more effective than the dialysis techniques currently used in preparative chemistry.[24] Similarly, the exchange of respiratory gas in both the placenta and the gill appears most efficient when operating on the principle of countercurrent exchange.[38]

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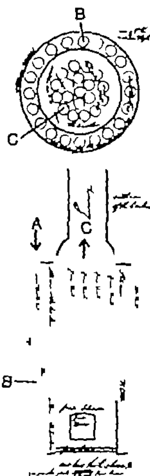


Fig. 1. Trevithick vertical tubular boiler. "The design is for the cold air to pass down from the top of the boiler (A) through the air tubes that round the boiler (B) and to get heated in its passage by condensing the steam in the case and to pass up through the fire case in the hot state (C)." (From Dickinson, H. W., and Titley, A., editors: Richard Trevithick, London, 1930, Cambridge University Press.)

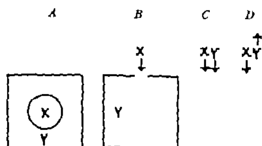


Fig. 2. Four ways in which two solutions (X and Y) equilibrate across a permeable membrane. *A*, No bulk flow in either solution. *B*, One-sided flow. *C*, Concurrent flow. *D*, Countercurrent flow.

Barrier effect produced by countercurrent exchange

In arctic conditions certain birds maintain central body temperature by short-circuiting heat from arterial to venous capillaries of a countercurrent exchanger (a rete mirabile) interposed in the vascular trunks of the leg.[61] The over-all effect is that of a countercurrent exchange barrier insulating the bird's warm body from its own cold feet (Fig. 3, *A*). Similar mechanisms have been identified in the mammal.[62]

Countercurrent exchangers may therefore equilibrate as in the placenta or separate as in the rete mirabile of the bird. The difference in function is related to the external circulation of the exchanger: one circulation only is connected to the barrier rete of the bird (Fig. 3, *A*). Heat exchanged within the mechanism thus returns to its source. In the countercurrent placenta, on the other hand, separate maternal and fetal circulations are juxtaposed (Fig. 3, *B*). As a result, maternal oxygen returns not to its source but to the fetus (carbon dioxide follows the reverse route at the opposite end of the exchanger). Thus, depending upon their external connections, countercurrent exchange may produce either a barrier effect

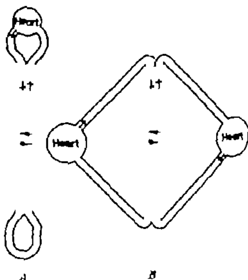


Fig. 3. *A*, Countercurrent barrier. A barrier effect produced by countercurrent exchange between two parts of the same circulation as in the heat-exchanging rete of the bird. *B*, Countercurrent equilibrator. An equilibration effect produced by countercurrent exchange between two different circulations, as in the placenta.

between two parts of the same circulation or an equilibrating effect between two different circulations.

Countercurrent multiplication

General characteristics. A second distinction among countercurrent mechanisms divides exchangers (barrier and equilibration in type) from multipliers. Functionally, the multiplier consists of two components: a hairpin loop and an energy-consuming process capable of establishing a small difference of concentration between the adjacent limbs of the loop (Fig. 4, A and B). Maintenance of this single-effect process while fluid flows round the loop leads to a *steep gradient of concentration in the long axis of the loop.*[24] The over-all performance of a *multiplier in creating a gradient is* to be contrasted with that of an exchanger which is capable only of *maintaining an existent gradient.*[25]

Analysis of the function of a multiplier poses two main questions: (1) Where is the loop situated? (2) What is the nature of the single-effect mechanism? In the swim bladder rete, perhaps the best understood multiplier to date, the loop is formed by blood vessels and the single effect is probably derived from a metabolic source of energy.[21 22 23 24] Although it is likely that the concentration of urine also depends upon countercurrent multiplication, neither the site of the loop within the medulla nor the mechanisms of the single-effect have been generally agreed upon.

Multiplication in the renal medulla. It is now well established that during dehydration a steep gradient of solute concentration extends throughout the renal medulla to reach a peak in or close to the papilla. Urine is then concentrated by the withdrawal of water from the collecting duct into this solute rich environment. Controversy surrounds the question of how in the first place a countercurrent multiplier enriches the solute content of the medulla. Several factors may be responsible for the uncertainty: two loops, for example, exist as potential candidates for the multiplier and although a *large number of single effect* mechanisms have been considered most are inaccessible to experimental study.

Any single-effect mechanism capable of producing urine more concentrated than

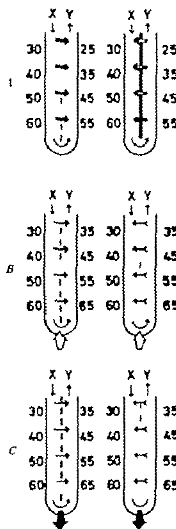


Fig. 4. Scheme in which hairpin loop might act as multiplier. Numbers denote arbitrary units of solute concentration. In each instance difference of solute concentration, the single effect, is created between the limbs of the loop. This difference will then be reduced by countercurrent flow of fluid. However, maintenance of the single-effect process with countercurrent flow leads to multiplication of solute concentration in long axis of loop. See text. A, "Single effect" created by movement of water through solute impermeable membrane as result of hydrostatic pressure. B, "Single effect" created by active transport of solute through water impermeable membrane. C, "Single effect" created by addition of solute to vertex of loop with subsequent transverse movement of water or (D) solute. F, "Single effect" created by removal of water from vertex of loop with subsequent transverse movement of water or (F) solute.

blood must separate water from solute in order to create the necessary difference of osmolality between the adjacent limbs of the loop. Four types of single-effect process have been discussed previously. (1) The first type is separation of water from solute by hydrostatic pressure forces in the loop of Henle[1] or in the vasa recta (Fig 4 *A*).[8,77] (2) The second type is active transport of sodium from the ascending limb of the loop of Henle (Fig 4 *B*).[17,37,78] (3) The third type is addition of solute to the vertex of the loop thereby establishing a gradient of osmolality between the adjacent limbs which then initiates multiplication by provoking either transverse water movement (Fig 4 *C*) and or transverse solute movement (Fig 4 *D*).[42] Considerable evidence now suggests that countercurrent multiplication of gas occurs in this way within the swim bladder rete.[27,44,54] (4) The fourth type is removal of water from the vertex of the loop. Multiplication is then initiated as above by the movement of either water (Fig 4 *E*) or solute (Fig 4 *F*).[42]

The composition of the solute gradient generated will vary from model to model. In multipliers operating by solute movement (active transport and solute diffusion) the gradient will consist of the diffusing or transported solute. In multipliers operating by water movement (hydrostatic pressure and osmotic water movement) the gradient will consist of all solute which is less permeant than water.[42] Other variables affecting the performance and efficiency of multipliers have been considered elsewhere.[7,41,72] Further types of countercurrent multiplier have been described by Kuhn and Ryffel[24] and by Niesel and Röskenbleck.[46] Coupled multiplier systems[42,44,45] are also of particular interest and will be considered in more detail subsequently.

In summary, countercurrent systems may equilibrate, separate, or multiply. As structural factors determine the type of effect achieved, anatomical investigation is essential in understanding a countercurrent process. This is particularly true of renal countercurrent mechanisms which may produce the solute concentration gradient by multiplication, maintain the gradient by a barrier effect, and promote the transfer of water and solute between the nephron and its adjacent capillary blood supply by an equilibration effect.

Anatomy of the renal medulla

The renal medulla may be divided into three zones (Fig 5): the subcortical zone (also known as the outer strip of the outer zone), the outer zone (also known as the inner strip of the outer zone), and the inner zone.

1. *Tubules*. The renal tubule consists of proximal and distal convoluted segments connected by a loop of Henle. In the rat, approximately two thirds of the loops are of the short type extending into the medulla to the junction of the inner and outer zones (Fig 5 *C*). The long loops pass for a vari-

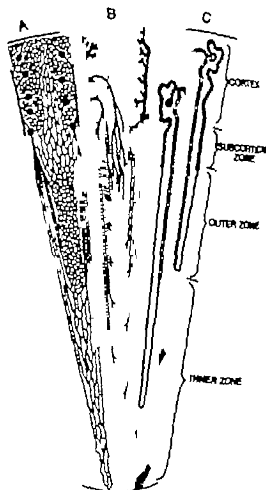


Fig 5. Schematic representation of a single section of the rat kidney in which three components are illustrated separately. *A*: The arterial and capillary blood supply. *B*: the venous drainage; *C*: collecting duct with one long and one short loop of Henle.

able distance into the inner medulla and of these a minority reach the tip of the papilla.[38] Approximately six distal tubules (two derived from long loops and four from short loops) unite in the cortex to form a collecting duct which passes through the medulla joining with other ducts and finally opening at the tip of the papilla.[38, 43]

2. *Blood vessels of the renal medulla* The blood supply (Fig 5) of the renal medulla[11, 34, 40, 71] is derived from efferent arterioles of juxtamedullary glomeruli. These

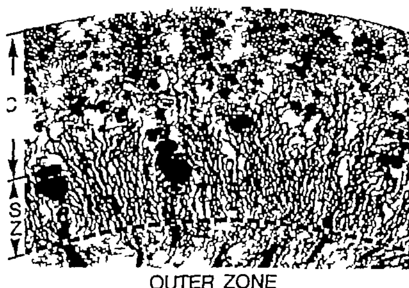


Fig 6 Vertical section of rat kidney after injection of colored gelatine showing conspicuous veins of subcortical zone (*SZ*). *C* stands for cortex. See reference 57 for details of technique (Magnification × 22.)

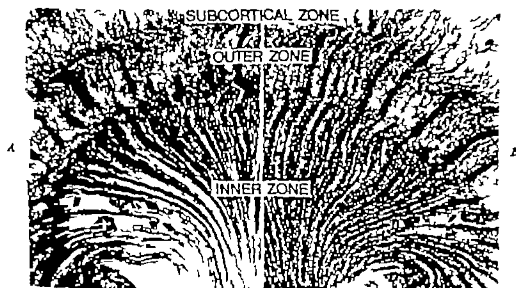


Fig 7 Two vertical sections of the rat kidney showing the vasa recta bundles of outer and inner zones. *A* following venous injection and *B* following arterial injection of india ink. See reference 57 for details of technique. *B* shows filling of capillaries (Magnification × 18.)

vessels divide in the subcortical zone to form arterial vasa recta which then pass through the medulla in cone-shaped bundles (Fig. 7). At intervals, arterial vasa recta leave the bundle to supply an adjacent capillary plexus (Figs. 8, *B* and 10, *H*). Arterial and venous vasa recta do not appear to unite directly. The capillary plexus is drained by venous vasa recta which enter the bundle and ascend to its base in the subcortical zone. Leaving the bundle, the venous vasa recta *ascend through the subcortical zone* in close association with collecting ducts and, to a lesser extent, with descending and ascending loops of Henle (Fig. 13). The venous capillaries which drain the plexus without entering the bundle (see Fig. 5) also appear to follow this route. Both groups of vessels empty into the arcuate and interlobular veins at the corticomedullary boundary (Figs. 5, *B* and 6). In the subcortical zone, the capillary plexus is supplied by arterial vasa recta and, more directly, by the branches of efferent glomerular arterioles.

The pattern of the capillary plexus differs in the three zones of the medulla (Fig. 5, *A*). In the subcortical zone it appears sparse and wide meshed, although the ascending venous vasa recta traversing the zone give the over-all impression of a dense capillary network (Fig. 6). In the outer zone of the medulla, on the other hand, the plexus is distinct from the vasa recta bundle and is

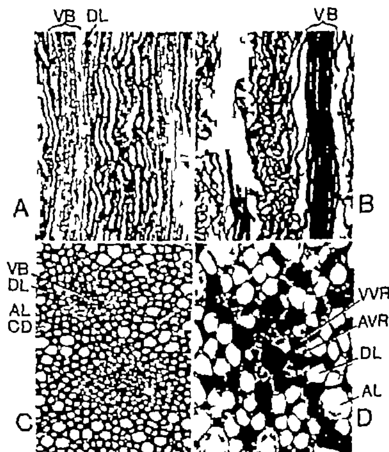


Fig. 8. Outer zone of rat kidney. *A*, Vertical section showing two vascular bundles (*VB*) with closely related descending loops of Henle (*DL*). *B*, as in *A* following arterial injection of India ink, showing the vasa recta bundles with connections to dense capillary plexus. *C* and *D*, transverse sections showing vascular bundle whose central core is composed of arterial (*AVR*) and venous vasa recta (*VVR*). Surrounding this zone, a peripheral ring in which thin descending limbs (*DL*) alternate with venous vasa recta. More peripherally still, a zone containing collecting ducts (*CD*) and ascending limbs of Henle's loop (*AL*). See also Fig. 9 for schematic representation. Details of technique in references 24 and 57. (Magnification: *A*, ×80; *B*, ×83; *C*, ×63; *D*, ×240.)

characteristically dense in form.[13] On entering the inner zone, it becomes less dense with long open meshes (Fig. 5, 4).

3. *Interstitial space and interstitial cells.* In the outer zone the tubules and blood vessels are closely packed; accordingly, the interstitial space appears sparse. This state of affairs reverses in the inner zone, particularly toward the papilla, where both interstitial space and interstitial cells seem most abundant.[7] The cells themselves are closely related to blood vessels and loops of Henle.[7, 39, 40] Their possible role in the urine-concentrating process will be discussed.

4. *Structural organization within the renal medulla.* The cone-shaped vasa recta bundles dominate the pattern of the renal

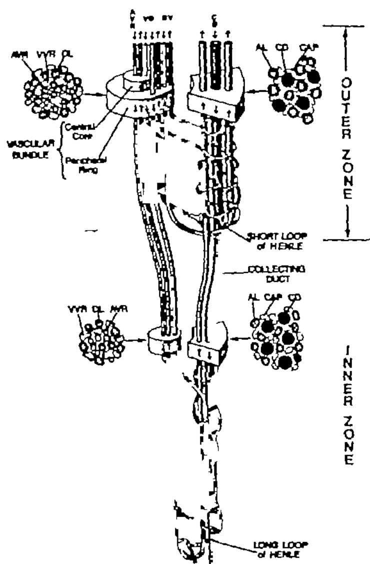


Fig. 9. Schematic representation of structures of inner and outer zones of renal medulla in ... A short loop of Henle is shown crossing between the bundle and the collecting duct in the outer zone. A long loop of Henle crosses in similar way in the inner zone. In addition, arterial and venous vasa recta pass between the bundle and the capillary plexus which surrounds the duct and the ascending limb of Henle loop. *AVR*, Arterial vas rectum; *VVR*, venous vas rectum; *DL*, descending limb of Henle loop; *AL*, ascending limb of Henle loop; *CD*, collecting duct; *CAP*, capillaries.

medulla [1,8] In the rat[3] they form the central axis of a unit which extends from the subcortical zone to the tip of the papilla (Figs. 7 8 and 10 *J*) In cross section of the outer medulla of the rat (Figs 8 *C D* and 9) the unit may be divided into three concentric zones (1) the central core of the bundle containing arterial and venous vasa recta (2) the peripheral ring of the bundle containing venous vasa recta and most of the descending loops of Henle and (3) outside this ring a zone containing three further structures, the ascending limb of Henle's loop the collecting duct and the capillary plexus.[23,24,25]

In the inner zone the bundle becomes progressively reduced in size (Fig 10 *J*) Although less clear than in the outer zone, its distinction from other structures is nevertheless apparent (Fig 10 *A*) Determination of the relative position of the two limbs of the loop of Henle is important from the standpoint of countercurrent theory In the outer zone ascending and descending limbs are systematically separated from each other (Figs. 8 and 9) In the inner zone the position is less clear as the two limbs are similar in microscopic form. An attempt was therefore made to establish their relative position First all structures crossing the boundary of the inner and outer zone were examined Each ascending limb identified in this way (by its abrupt transition to thick walled form) was found to be closely related to a collecting duct in its ascent from the inner zone (Fig 10 *F*). In the second method complete long loops (of the shorter variety) were followed in vertical section through the inner zone. Here again the ascending limb was found

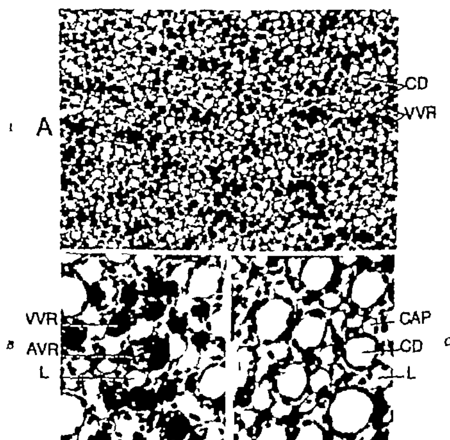


Fig 10 *A B* and *C* Inner zone of rat kidney *A* Transverse section after clamping renal vein showing separation of groups of collecting ducts (*CD*) from prominent venous vasa recta (*VVR*). (Magnification × 80) *B* Transverse section of vascular bundle showing arterial (*AVR*) and venous vasa recta (*VVR*) with thin (probably descending) limb of Henle loop (*L*). (Magnification × 290.) *C* Transverse section of a group of collecting ducts (*CD*) associated with capillaries (*CAP*) and thin limbs (probably ascending) of Henle's loop (*L*). (Magnification × 330.)



Fig. 10 *D*, *E*, and *F*. Inner zone of rat kidney. *D* and *E*. Two adjacent vertical sections showing a single loop of Henle (*L*) descending from the region of the vascular bundle (*VB*), reversing and ascending (*AL*) in close association with the collecting duct (*CD*) to the boundary of the inner and outer zones (*BZ*) where it assumes thick walled form (*TW*). (Magnification × 75.) *F*. Vertical section showing a group of closely related ascending loops of Henle (↑) and collecting ducts (*CD*) at the boundary of inner and outer zones (*BZ*). (Magnification × 180.)

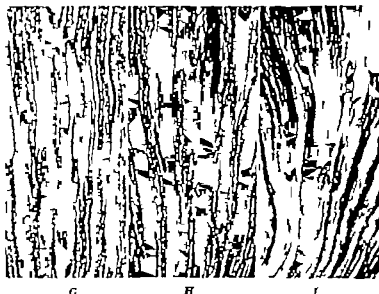


Fig. 10 *G*, *H*, and *I*. Inner zone of rat kidney. *G*. Vertical section showing lines and parallel relation between adjacent structures in the inner zone. (Magnification × 75.) *H*. Arterial injection of India ink showing vasa recta bundles with intervening capillary plexus; vertical section. (Magnification × 40.) *I*. Venous injection of India ink showing vasa recta bundle in vertical section. (Magnification × 40.)

to be closely related to the collecting duct (Fig 10 *D* and *E*) Descending limbs on the other hand were never found in association with collecting ducts or with their own ascending limbs in each instance they appeared to pass through the inner zone closely related to venous vasa recta (Fig 10 *B*) Collecting ducts were more closely associated with ascending loops of Henle in the inner than in the outer zone

The anatomical findings suggest therefore that in the rat kidney loops of Henle descend through the outer zone in association with venous vasa recta Short loops turn laterally in this zone and rise through the capillary plexus (Fig 9) Long loops of Henle descend further with venous vasa recta into the inner zone before turning to ascend in close association with the collecting duct and capillary plexus (Fig 9)

Functional effects suggested by the anatomical findings

1 *Countercurrent mechanisms* Countercurrent processes might be expected to occur where descending and ascending tubes are juxtaposed Three such pairs have been demonstrated (1) ascending and descending vasa recta (Fig 8 *D*) (2) venous vasa recta and descending loops of Henle (Fig 8 *D*) and (3) ascending loops of Henle and collecting ducts in the inner zone (Fig 10 *C D E* and *F*)

If countercurrent effects occur in these sites the type of effect (multiplication equilibration or barrier) will to some extent be determined by the double or single nature of the circulation involved (see Fig 3) As the ascending descending vasa recta pair are part of the same circulation a barrier and or multiplication effect is most likely The other pairs are each composed of two circulations. Equilibration would therefore be their most likely countercurrent effect

2 *The bundle as a central countercurrent system* The bundle with its central core and peripheral ring (see Fig 9) may act as a central countercurrent system linked to the collecting duct by loops of Henle and by arterial and venous vasa recta The overall arrangement is illustrated schematically in Figs. 9 and 11 As an illustration of the way in which the system might work, consider the sequence of events following the addition of diffusible solute to the interstitial space of the inner zone (Y in Fig 11). The solute would diffuse into capillary blood enter the central system in venous vasa recta and rise toward the cortex. Within the bundle, the solute would undergo countercurrent transfer both to descending vasa recta and to descending loops

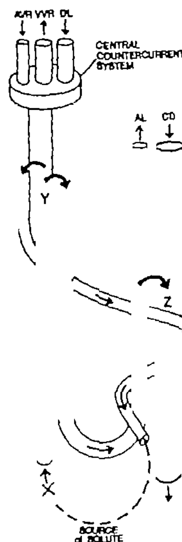


Fig *11* Schematic representation of the way in which solute added to the inner medulla may return to its source. Thick arrows represent the direction of hyperosmotic effect which may be solute movement in direction of arrow or water movement in the opposite direction *CD* Collecting duct *AL*, ascending limb of Henle's loop *DL*, descending limb of Henle's loop *AVR*, arterial vasa recta *VVR*, venous vasa recta. Solute added at *Y* undergoes countercurrent exchange at *X* to descending loop of Henle and to descending vasa recta. Both subsequently equilibrate at *Z* with collecting duct the loop by countercurrent exchange and the vessel possibly by concurrent exchange.

of Henle In either event it would leave the central system in a transverse bridge and return toward its source in the inner zone Thus, the loop of Henle and the arterial vasa recta may serve as a functional bridge between the central countercurrent system and the collecting duct. The further possibility that blood vessels may link functionally separated limbs of the loop of Henle will be considered in a later part of this paper

3 *Segmental bridges in the inner zone* Vasa recta as well as loops of Henle appear to pass at regular intervals between the central countercurrent system and the collecting duct in the inner zone (Fig 12) Injection studies[2, 47] suggest that blood in the plexus surrounding the collecting duct flows downward toward the papilla. In this event, the duct would be exposed to segmental and concurrent flow of arterial capillary blood In certain respects, this

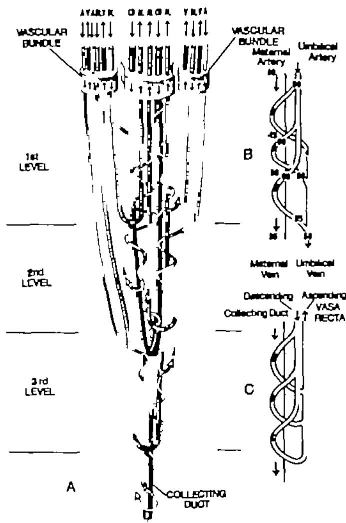


Fig 12 A Schematic representation of the relation between the vascular bundles and the collecting duct At each of the three levels illustrated the collecting duct (*CD*) and bundle are linked by loop of Henle and by arterial (*A*) and venous vasa recta (V) The capillaries are denoted by coiled tubes. *B* Diagram of ... ous flow system (Bart ... and Met ...) ... fetal and maternal blood equilibrate in ... series of three units Arbitrary figures of gas partial pressure have been chosen to illustrate the point that ... series of equilibrating units ... the gas pressure (CO_2) ... the maternal ... at higher level than that ... the umbilical vein. *C* Diagram of segmental blood supply to collecting duct The ... ascending and descending vasa recta are shown schematically as single trunks.

arrangement resembles the segmental multivillous or multicapillary systems of the placenta and gill[1,49] the efficiency of which is greater than that of a simple concurrent exchanger (see legend to Fig 12 *B*) The vascular bridges between the central countercurrent system and the collecting duct may have a similar effect in that fluid within the duct would be subjected to a series of concentrating effects (Fig 12 *C*)

Relation of anatomical findings to theories of urine concentration

If as seems probable urine is concentrated by countercurrent multiplication analysis of the process will turn on two questions location of a countercurrent loop and the nature of its associated single effect mechanism The purpose of this section is to consider both questions in relation to the anatomical observations discussed earlier

1 *The loop of Henle active transport theory* In perhaps the most widely accepted theory of the urine concentration mechanism the role of multiplier has been attributed to the loop of Henle. According to one version of this view[14,37,72] sodium actively pumped from ascending limb fluid increases in concentration in the peritubular space diffuses toward and into the descending limb and thereby establishes a difference in sodium concentration and osmolality between the limbs of the loop (Fig 4 *B*) Continued pumping of sodium and countercurrent flow then leads to multiplication In this model diffusion of sodium from the peritubular space of the ascending limb to the lumen of the descending limb will depend in part on the proximity of the two limbs On theoretical grounds, multiplication may occur when the limbs of a countercurrent loop are separated.[17] However efficiency of multiplication decreases with increasing separation[17] and is further reduced by the interposition of structures preventing free diffusion In known countercurrent systems, the ascending and descending tubes are usually closely related in regular geometrical patterns.[61] The loop of Henle is not arranged in this way The systematic separation of its ascending and descending limbs strongly suggests that the loop does not act as a multiplier with diffusion of solute between its limbs. This objection applies to a commonly held view of the multiplier (Fig 4 *B*) It does not apply to models in which the limbs of the loop are bridged by capillary circulation or to those in which the loop pumps sodium into the inner zone to produce a single effect which is then multiplied by circulation through other loops

THE LOOP OF HENLE IN THE OUTER ZONE. In the outer zone the limbs of the loop of Henle are bridged by a capillary circulation (Fig 9) Sodium pumped from the thick ascending limb[73] may therefore enter the capillary plexus and pass by venous vasa recta into the vascular bundle. It would then be transferred into the descending limb of the loop and into the descending vasa recta thereby returning to the ascending limb of the loop of Henle and its surrounding capillary plexus. In this way a single effect might be propagated by a capillary portal circulation. The loop of Henle would then act as a multiplier producing a gradient of solute concentration within the outer zone Pinter and Shohet[4] have previously suggested that the thick ascending limb of the loop of Henle might act as a multiplier in association with vasa recta The mechanism outlined here is identical in this respect but differs in its anatomical form. Unlike Pinter's proposal, it does not imply that a gradient of concentration might extend into the inner zone[14,65]

THE LOOP OF HENLE IN THE INNER ZONE. The single effect mechanism responsible for the final concentration of urine is likely to be located within the inner zone.[22,23] The loop of Henle in this site is thin walled and without either the histological[17,48,55] or the electrical[17] characteristics of an active transport process. Such minor differences as have been shown by electron microscopy are the opposite of the prediction that the ascending limb is the more active member of the pair Doubts have therefore been cast on the ability of the loop to play the necessarily active role in producing a single effect On the other hand micropuncture of the loop in this site[21] has shown that the osmolality of ascending fluid is reduced relative to that in the descending limb at the same level As the authors suggest the difference in osmolality may result from the active pumping of sodium from

the thin ascending limb However the opposite explanation of their finding—dilution of ascending limb fluid by water influx—is suggested by direct observation of the loop in vivo[67,70] In our view the evidence indicates that the thin ascending limb of the loop of Henle lacks one and possibly both of the characteristics essential to a sodium pump single-effect the pump itself and water impermeability of the tubular walls. Should this view prove incorrect and the thin limb be shown capable of producing a "single-effect, its subsequent multiplication would be unlikely to occur in the loop of Henle alone. A more likely mechanism will be discussed shortly

2. *The vasa recta* On morphological grounds, the vasa recta seem a likely site for a multiplier the pattern of closely related ascending and descending vessels[23] is very similar to that of the swim-bladder rete a known countercurrent multiplier[38] Furthermore, considerable evidence[71] now supports the proposal[1,72] that these vessels act as a countercurrent exchanger maintaining the solute gradient of the renal medulla. That they should also act as a multiplier using hydrostatic pressure as a source of energy[31] has been disputed on the grounds that ultrafiltration by pressure would be unlikely to yield an adequate single effect.[72] This objection does not, however apply to multiplication by the vasa recta of a single effect produced by means other than ultrafiltration.

3 *Other possible mechanisms of the "single-effect*

REMOVAL OF WATER BY MUCOPOLYSACCHARIDES. Polysaccharides have been linked to the urine concentration mechanism in several ways.[31,73] Recently Pinter[4] has suggested that mucopolysaccharides may raise the osmolality of the inner zone by binding water to a relatively greater extent than solute Disposal of the water loaded polymer possibly in ascending vasa recta blood would then lead to a continuous concentrating effect, provided (1) that the binding capacity of the polymer exceeded the reduction of osmolality associated with its synthesis, and (2) that the polysaccharide was synthesized continuously within the zone. Multiplication could then occur in the manner illustrated in Fig 4 *E* and *F* The ability of polysaccharide to bind water is well recognized[30,41,42] Chemical and histological studies suggest that the polymer is present in large amounts within the inner zone and that the interstitial cells may be responsible for its synthesis.[12,17,34] However as Pinter[4] has pointed out it remains to be shown that a polysaccharide mechanism can bind sufficient water to produce an adequate single effect."

SOLUTE PRODUCED OR RELEASED WITHIN THE INNER ZONE. Solute produced or released within the inner zone may lead to countercurrent multiplication by the diffusion of water (Fig 4 *C*) or solute (Fig 4 *D*) between the limbs of a countercurrent loop[47] Solute production might occur in several ways by lysis of arginine to ornithine and urea,[43] by hydrolysis of protein to amino acids,[44] or by the formation of lactic acid from glucose by anaerobic glycolysis.[45] Although lactic acid is present in an increased amount in vasa recta blood[49] medullary lactate does not vary during changes in urine flow[4,49] in a way which suggests a role for the substance in producing the solute gradient. Moreover none of these mechanisms can explain the fact that several solutes are known to be concentrated together within the renal medulla.

HYPOOSMOTIC REABSORPTION FROM THE COLLECTING DUCT Solute and water are reabsorbed from the collecting duct[5] osmotic forces being generally held responsible for the relative excess of water reabsorbed during dehydration. Alternatively Marsh and his colleagues[36,37] have recently suggested that excess water reabsorption may be coupled to active sodium transport The process was described as lineal rather than countercurrent multiplication. As a result of such hypoosmotic reabsorption fluid within the duct becomes concentrated while fluid in the space surrounding the duct becomes slightly less concentrated than that within the duct at each level The present anatomical studies are relevant to this proposal n suggesting that the countercurrent diffusion of watery reabsorbate directl from the collecting duct into the adjacent ascending thin limb of the loop of Henle would increase the over-all efficiency of the mechan m by reducing the amount of water added to the ner zone

4 *Vasa ecta–loop–collecting duct complex*

as the possible site of a multiplier In the light of the anatomical findings discussed earlier neither the loop of Henle nor the vasa recta seem likely to act alone in a concentrating mechanism A more likely site for a multiplier is represented in Fig 11 Assume for the purpose of illustration that some continuously operating process (see earlier discussion of candidates for single-effect mechanism) leads to a small increase in the solute content of interstitial fluid in the innermost part of the inner zone (*Y* of Fig 11) This will raise the osmolality of capillary and venous vasa recta blood By countercurrent exchange osmolality will then rise in descending vasa recta blood and in fluid within the loop of Henle and the collecting duct (*Z*) In this way the increment of solute concentration returns to its source in the inner zone and becomes the background for a further increment of solute concentration Multiplication would then be initiated Niesel and Röskenbleck[41] have previously discussed a similar principle in relation to a different arrangement of medullary loops

The proposal outlined in Fig 11 implies that osmotic equilibria are more likely to be established between pairs of related structures than between structures which are separated from each other but are nevertheless within the same transverse plane The recent micropuncture data of Jamison and associates[27] lend some support to this view Significant differences of osmolality were found between three pairs of unrelated structures (1) ascending and descending limbs of Henle's loop (2) descending loops of Henle and descending vasa recta (at fast but not at slow rates of flow) (3) descending vasa recta and ascending loops of Henle (at slow but not at fast rates of blood flow) In contrast the differences of osmolality found between the ascending vasa recta and the descending loop of Henle a related pair were small and insignificant.

5 *The possibility of different concentrating effects in the inner and outer zones* Although the solute gradient extends throughout the renal medulla separate (but not necessarily different) concentrating effects may be present in the inner and outer zones.[12, 51] In such an event separate single effects could be multiplied at different levels of the medulla by the central countercurrent system Thus a single effect produced within the outer zone could be multiplied because it returned via the central system to its point of origin An inner zone "single effect" could be multiplied at a different level of the same central system to produce a gradient within the inner zone (Fig 9)

6 *Water reabsorption from the collecting duct* The relation between the collecting duct and the mechanism producing the solute gradient to the renal medulla is important. Several types of association have been considered in the past.[17, 37] In the simplest model ducts, loops, and blood vessels are randomly arranged throughout the medulla. Thus, water reabsorbed from the duct would have an equal opportunity of equilibrating via the interstitial space, with each of the ascending and descending vascular and nephron loops. Although widely accepted this view of the concentrating mechanism has no anatomical basis. Furthermore as discussed above, differences of osmolality between structures at the same transverse level may be related to their anatomical separation

Kuhn and Ramel[37] have considered different models in which the duct might be more specifically associated with either the ascending or the descending limb of a multiplier (the loop of Henle in their analysis) In these arrangements water would be withdrawn by countercurrent or concurrent diffusion from the collecting duct into the multiplier itself

Our own proposal (Fig 11) is similar in principle in that the duct equilibrates with the inner zone not directly but via the loop of Henle and the capillary plexus. In this way the loop acts not only as a source of hyperosmotic fluid for equilibration with the duct, but also as a sluice for water reabsorbed during the process of equilibration A role for the loop of Henle in removing excess water from the renal medulla has been suggested previously[43, 54] This function of the thin ascending limb is unlikely to extend to the outer zone as the duct and the thick ascending loop are less closely related in this site.

7 *Subcortical zone* From an anatomical point of view the most striking structures of the subcortical zone are the venous vessels (derived from ascending vasa recta and from veins draining the capillary plexus



Fig. 13. Transverse section of the subcortical zone of rat kidney with clamped renal vein showing association of venous vessels (VVR) with collecting ducts (CD) and ascending (AL) and descending limbs (DL) of Henle loop. (Magnification × 210.)

Figs. 5 B and 6). The vessels appear to rise singly toward the cortex in close association with renal tubules, particularly with the collecting duct and descending thick limbs of the loop of Henle (Fig. 13). As the entire venous drainage of the medulla follows this route, solute may be conserved within the medulla by countercurrent exchange from venous vasa recta blood into the collecting duct and descending loop of Henle, a process similar in principle to lagging the hot gas output of a furnace with its cold air input (Fig. 1).

8. *Anatomical data and urine concentration mechanisms.* If urine is concentrated by countercurrent multiplication, anatomical data are of most use in locating the countercurrent loop. For reasons which have been discussed, it seems unlikely that a "single effect" is propagated between the limbs of the loop of Henle by simple diffusion (Fig. 4 B). These doubts do not apply to alternative roles for the loop as part of a multiplier (see earlier discussion). Similarly, although the vasa recta might act as a multiplier, they are unlikely to do so in isolation from the descending limb of the loop of Henle. Most likely from an anatomical point of view is the proposal that a series of linked countercurrent processes lead to multiplication (Fig. 11). The identity of a "single-effect" mechanism has not been established. Different concentrating processes may be present in the two zones.

9. *Summary and opinion on countercurrent mechanism.* Our present view of the urine concentration mechanism is as follows: first, that the process almost certainly depends upon countercurrent multiplication in the widest sense of the term (i.e., one of the mechanisms described in Fig. 4); second, that it is most profitable to analyze the mechanism from two separate standpoints: the anatomical question of the site of countercurrent multiplication and the physiological problem of the "single effect." As regards the site, we feel it more likely that multiplication occurs within a vasa recta–loop of Henle complex (Fig. 11) than in any site hitherto proposed. Anatomical data are less helpful in analysis of the "single effect." We have no distinct preference for any of the "single-effect" mechanisms considered earlier, as none is overwhelmingly supported by experimental data.

Pathological countercurrent mechanisms

Normal countercurrent processes may be deranged by disease. Thus, the failure to concentrate urine in sickle cell trait and in potassium depletion may result from interference with an existent countercurrent mechanism.[n, n, n]

Alternatively, countercurrent processes may lead to disease: renal papillary necrosis following phenacetin, for instance, may result from retention of the drug by countercurrent exchange within the papilla.[n] Similarly, the calculi of hyperparathyroidism (and possible other states) may be a consequence of abnormal countercurrent trapping of calcium within the renal medulla.[n] Countercurrent exchange of heat probably occurs normally in the peripheral circulation of man. Its extent might, however, become abnormal. Frostbite and Raynaud's phenomenon, for example, could result from an abnormally efficient exchange of heat between peripheral arteries and veins. It may be relevant that reduction in the rate of flow through a countercurrent exchanger increases the efficiency of exchange[n, n] and that a predisposition to Raynaud's phenomenon may be present in states (such as arterial obstruction and syndromes with increased blood viscosity) where peripheral blood flow is reduced.

Summary

Countercurrent processes are highly effective means of promoting or preventing

equilibration between two environments By circulation through a loop they may also multiply a small single effect into a steep gradient of concentration While it is probable that countercurrent effects occur in many biological situations, analysis of the mechanisms involved has not proved simple. This is particularly evident in the kidney where the existence of several potential sites for countercurrent processes has complicated their separate analysis. Most recent theories of urine concentration are based on the principle of countercurrent multiplication Whatever the merits of these ideas, none has been as clearly confirmed as the principle underlying Trevithick s boiler (Fig 1)

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Fundamentals of clinical cardiology

Viral valvulitis

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Acquired chronic valvular heart disease has traditionally been thought of as due to rheumatic fever with an associated streptococcal infection. Nevertheless, some of the early epidemiologic studies of the relationship of streptococcal infection to the rheumatic state revealed patients who failed to give a history of acute streptococcal infection or rheumatic fever preceding the onset of valvular heart disease. This group of patients has been largely ignored. With time most physicians developed the clinical policy of using such nonspecific terms as subclinical or occult rheumatic fever to explain those instances in which patients presented with evidence of chronic valvular disease but without an antecedent history of acute rheumatic fever. That there are instances of mild or unrecognized episodes of a rheumatic process following a streptococcal infection is most likely. However, the incidence of this situation is probably much less than is presently recognized. Furthermore, for clinical purposes it seems more desirable to identify a specific etiologic factor where possible for acute or chronic valvular disease than to state merely that an antecedent rheumatic fever was subclinical, occult, or unrecognized.

Because of our interest in heart muscle disease and in the etiology of valvular disease over the past few years, we have studied the possible etiologic relationship of viral infections to disease of the heart.[1-3] Our initial interest was directed toward acute and chronic muscle diseases that could be produced in the experimental animal with a number of viruses of the picornavirus group. Of these the Coxsackie B strains seemed to exhibit definite cardiotropism in the mouse and monkey. A survey of myocardial tissues from over 1,000 human autopsies demonstrated that viral antigen could be detected by immunofluorescent techniques in patients dying of a number of causes (unpublished data). The recognition that this group of viruses could produce acute myocarditis and pericarditis in man is not new and has been reported a number of times, especially in the pediatric literature.[4-] Early experiments on suckling mice and monkeys in our laboratory, however, showed that, aside from the expected myocarditis and pericarditis, acute valvulitis and mural endocarditis were often important accompaniments of the infection.[3] These observations prompted us to look more extensively into the pathogenesis of acute and chronic valvular lesions and the long term consequences of viral valvulitis.

Chronic experiments were initiated in cynomolgus monkeys, which were designed to determine the long term effects of Coxsackie B viral disease. It was found that gross and microscopic valvular endocar-

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dial and myocardial lesions occurred in animals studied over periods as long as 200 days after the initial intravenous inoculation with Coxsackie virus B_4.[9] These lesions exhibited a striking similarity to those of rheumatic fever. Fibrotic thickening of the valve leaflets, fibrosis and shortening of the chordae tendineae, Anitschkow's myocytes, Aschoff-like bodies, and other so-called characteristic morphologic changes were among the most common lesions produced. In all instances immunofluorescent Coxsackie virus B antigen could be demonstrated in the valves, myocardium, and pericardium.

In reviewing the literature relative to viral valvulitis, one is impressed by the scarcity of information regarding this lesion. Occasional valvular lesions have been recorded by virologists, but presumably because of the nature of their interests and investigations, the topic of viral valvulitis has received little or no attention. For example, Miller and Andrews[1] studied Virus III, accidently isolated by Rivers and Tillett[12, 13] from rabbits. They were interested in myocarditis and the Aschoff lesion but ignored the valvulitis produced by this highly cardiotropic virus of rabbits. Pearce[14] was interested in the cardiac lesions of Virus III in rabbits and, although he also produced valvulitis in his rabbits with the virus, his attention was directed primarily toward the myocardial lesion.

Studies in Pearce's laboratory were probably the first clear demonstration that certain *conditioning factors* can play an important role in initiating myocardial and endocardial damage in experimentally infected animals. Pearce had been concerned with pathologic studies requiring the passage of Virus III intratesticularly in rabbits. In order to obtain control serum prior to inoculation, cardiac puncture was routinely performed. Because of a basic interest in the heart, the animals were autopsied and the heart examined 4 to 6 days after inoculation. Surprisingly, many animals whose hearts had been punctured exhibited an extensive pancarditis. The intranuclear inclusions typical of Virus III were readily identified and virus could be cultured from the myocardium without difficulty.

Virus III infection is usually a self-limiting asymptomatic infection in rabbits and is rarely fatal. It produces sporadic myocardial lesions in infected animals, which can be identified by fairly typical inclusion body formation and cytopathic effects. When introduced into susceptible animals without previous manipulations, Virus III produced cardiac lesions in approximately 25 per cent of cases. If it was injected into animals that have had cardiac puncture prior to introduction of the virus, the incidence of cardiac lesions increased to greater than 86 per cent.[14]

Besides preinoculation cardiac puncture, Pearce found that intravenous injection of gum acacia and small repeated doses of Pitressin caused a significant increase in the incidence and severity of myocarditis when the virus was subsequently introduced. The incidence of myocardial lesions in acacia-treated rabbits was greater than 94 per cent. From these observations the concept was developed that a number of pre-stress or conditioning factors could be introduced which would cause a usually mild or asymptomatic infection to express itself as a fulminant or more virulent process than would normally be expected.

Although Pearce noted in this series of studies that mural endocarditis and valvulitis were frequently present along with the myocarditis, he failed to emphasize the importance of these lesions. Of the 17 acacia-treated animals, 13 showed acute mural endocardial lesions and 7 of these 13 showed valvular lesions. The valvular lesions consisted of thickened fibrotic leaflets, inflammatory cell infiltration, inclusion body formation, hemorrhages, and fibroblastic proliferation. The chordae tendineae were frequently diffusely thickened and contracted and showed inflammatory cell infiltration. Had these animals been allowed to survive for a longer time, a typical fibrotic and scarred valve would probably have resulted. Other conditioning factors probably also predispose the animals to valvular damage but to a lesser extent.

These studies of conditioning factors are emphasized here because of their possible relationships to cardiac disease in man. Viral disease of the heart is too often ignored or not even realized. Conditioning factors, however, must influence the incidence and severity of cardiac disease due

to most, if not all infections of the heart Furthermore, it must be remembered that the valves knock against each other with great force with each heart beat especially when the blood pressure is elevated Physical trauma, infection and other stresses could function as conditioning factors which determine the development of viral valvulitis.

Pearce[11] subsequently investigated five more viral agents for their ability to induce acute cardiac lesions in acacia prepared animals. Vaccinia virus, pseudorabies virus, inflammatory fibroma virus, myxoma virus, *and strain A fibroma virus all produced* myocardial and endocardial lesions. Only the vaccinia pseudorabies, and inflammatory fibroma viruses, however produced valvular lesions.

Seventeen years after Pearce's first report brief mention of endocarditis with photomicrographs of valvular and endocardial inflammation was reported in two African mongooses infected with the EMC virus.[17] The study however was part of a larger group of investigations designed to study the pathogenesis and natural modes of transmission of this virus in the vicinity of Entebbe, Uganda and consequently the implications of this finding were not fully appreciated nor exploited Despite the route of infection (oral or intraperitoneal) all of the 9 infected mongooses developed severe myocarditis and eight showed pericardial or pleural effusions at autopsy

Lou and associates while studying the myocardial and central nervous system pathology of Coxsackie virus B in cynomolgus monkeys, noted that two out of 9 monkeys had an acute mitral valvulitis when sacrificed. One photomicrograph showed the mitral valve to be heavily infiltrated with inflammatory cells in a monkey sacrificed 28 days after infection. These investigators, however failed to pursue a study of these lesions, probably because of the nature of their interest and objectives.

We deliberately initiated a study of the possible role of viruses in the production of myocardial and especially valvular heart disease. Thus, in our laboratory experimental valvulitis has been produced in mice and monkeys. It was produced in 6 of 7 monkeys infected with Coxsackie virus B Grossly lesions consisted of verrucous aortic valvulitis (2 animals) verrucous mitral valvulitis (3 animals) and cicatricial thickening of the mitral valve leaflets and chordae tendineae with commissural adhesions (stenosis–2 animals) Histologically valve tissue displayed stromal edema round cell infiltration fibrocyte proliferation increased basophilia, and swelling of endothelial cells. Viral antigen was localized by immunofluorescent techniques in the damaged valve tissue. The lesions observed in these monkeys were similar to those so well known in human rheumatic valvular disease. *Immunofluorescent viral* antigen was identified in the valves as long as 200 days after inoculation of the monkeys.

In a study of 40 young mice injected intraperitoneally with Coxsackie virus B valvulitis was produced in 55 per cent of the infected animals. The damaged valves were tricuspid 43 per cent mitral 23 per cent aortic 10 per cent and pulmonic 5 per cent. The valvular lesions consisted of endothelial proliferations, round cell infiltration and edema Coxsackie virus B was recovered as late as 8 days after inoculation.[19] Immunofluorescent viral antigen was localized in the valves of these mice

In another study of mice viral antigen was noted in the tricuspid valve as early as three days after infection These valves showed intense granular cytoplasmic fluorescence. Endothelial cells, however did not display fluorescence at this stage. One week after inoculation viral antigen was noted in tricuspid and pulmonary valves, and seven days post infection viral antigen was detectable by immunofluorescent staining in the endothelial cells of the valves and mural endocardium High concentration of viral antigen was noted at the base of the tricuspid valves. Occasionally weak fluorescence was noted in the mitral and aortic valves. Mononuclear cell infiltration was prominent at the base of the affected valves.

By the second week of infection viral antigen was quite prominent in the aortic and mitral valves of the infected mice Antigen was mainly localized within the endothelial cells or deep in the stroma of the valves. Hematoxylin and eosin staining indicated that the cells in the fluorescent

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has yet to be adequately elucidated. It appears to us that many instances of chronic valvular heart disease in man may well be viral in origin. That viral antigen can apparently remain in situ for many years seems highly likely. We have observed immunofluorescent Coxsackie viral antigen in the myocardium from 1/ to 55 patients at routine autopsy at the Charity Hospital in New Orleans.[24] It is our opinion that in some instances a virus may be latent or dormant in valvular or myocardial tissue and later become activated by a specific conditioning factor to produce clinically overt illness. It seems quite plausible that in certain instances a streptococcal infection itself may be such a conditioning factor.

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Atropine in the treatment of cardiac disease

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Atropine, the most familiar of the belladonna alkaloids, has been used in clinical medicine for many years. Recently there has been new interest in this agent, particularly in treating patients with marked bradycardia. In some patients, prompt atropine therapy may avert the need for isoproterenol or pacemaker therapy. This review is intended to clarify the current role of the drug.

Clinical pharmacology

Atropine blocks the effects of acetylcholine at neuromuscular end-plates and synaptic junctions. Postganglionic parasympathetic receptor sites are most susceptible to this blocking effect, ganglia and skeletal neuromuscular end plates far less so. This variability has not been adequately explained. The drug is absorbed from all mucous membranes except the stomach. For cardiac purposes atropine should be administered parenterally, as gastrointestinal absorption is erratic and slow. Atropine apparently is partially detoxified in the liver; approximately 50 per cent is excreted unchanged in the urine within 24 hours of administration, most of this during the first 4 to 8 hours.

When intravenous atropine is given in therapeutic doses (4 to 2 mg) over a 30 second period, the sinus rate increases maximally during the ensuing 3 to 5 minutes. This effect lasts for approximately 2 hours. When atropine is given in small doses, or by slow intravenous or subcutaneous administration, paradoxic slowing of the heart rate may occur. There is evidence that this cardiac slowing is mediated via both central and peripheral mechanisms. Perfusion of the isolated central nervous system with atropine causes persistent cardiac slowing. The transient bradycardia following systemic atropine administration may be caused by initial stimulation at acetylcholine receptor sites. Apparently atropine competes with acetylcholine at these sites, causing an initial stimulation at low dose levels. Tachyphylaxis to the drug may occur, although it has not been a problem clinically.

Aside from the paradoxic cardiac slowing, atropine has few dangerous effects on the heart. Varying degrees of atrioventricular block and dissociation and occasional ventricular premature contractions have been reported. Anesthesia appears to potentiate the arrhythmic effect of the drug. In a large series of patients during halothane anesthesia, 17 per cent developed ventricular arrhythmias. When cyclopropane was used in conjunction with atropine, 50 per cent of the patients had ventricular arrhythmias; there was one episode of ventricular fibrillation.

There have been many careful studies of the hemodynamic effects of atropine. In the normal individual, rapid intravenous

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infusion of 1 to 2 mg of atropine produces a consistent rise in pulse rate and fall in stroke volume In most subjects cardiac output rises significantly during the first several minutes following administration when a steady state is achieved cardiac output returns to control levels. In recumbent patients no significant change in left ventricular systolic pressures occur although right atrial pulmonary artery and pulmonary wedge pressures may fall slightly The fall in right atrial and pulmonary wedge pressures may be due to decreased ventricular end-diastolic pressure accompanying increased heart rate and decreased filling time Apparently the diminished right heart pressures are not a result of peripheral venous pooling

The hemodynamic effects of atropine and concomitant infusion of 25 to 50 Gm of salt-poor albumin in 200 to 400 c.c. of normal saline have been studied In these patients, there was a marked increase in stroke volume with no significant change in right atrial pressures. These observations suggest a possible role for atropine in bradycardic patients with low output states, especially those with elevated venous pressures Limited studies in such patients during acute myocardial infarction have indicated that atropine is indeed beneficial. Not only does the heart rate rise, but stroke volume is maintained and therefore cardiac output is often markedly improved.

In normal recumbent patients, the hemodynamic effects of rapid atrial pacing and atropine-induced tachycardia are comparable. In both situations, there is little rise in cardiac output or change in blood pressure. Stroke volume and mean systolic ejection rate vary inversely with heart rate. These observations imply that in normal resting individuals, the effects of atropine are secondary to the increased heart rate Similarly atropine increases myocardial oxygen consumption, but only in proportion to its cardioacceleratory effect. This situation may not be comparable to th effects on patients with acute cardiac ill nesses in whom increased parasympathetic activity may be present. In this reg rd there has been considerable controversy concerning vagal influence on ventricular function Vagal stimulation, reportedly may depress atrial and ventricular contractility If this is true the rationale for atropinization has added validity

Atropine has been used experimentally in combination with propranolol to produce a heart unresponsive to sympathetic and parasympathetic stimuli Cardiac responses in such patients are comparable to those seen in denervated hearts and serve as interesting experimental models. Following exercise for example there is an increase in stroke volume with no significant change in heart rate Some investigators have suggested that atropine blocks the hemodynamic effects of propranolol However in the stressed or decompensated heart, atropine will not reverse the effects of propranolol.

While atropine has many noncardiac effects, most are not important when the drug is used parenterally in the acute therapy of cardiac patients. There is lessened bronchial tone which does not alter vascular dynamics significantly Diminished sweating may raise fever while the gastrointestinal effects cause diminution of motility and secretory functions. These side effects are usually not troublesome. Diminished bladder tone may lead to urinary retention Patients with glaucoma should receive atropine cautiously if at all. In large doses atropine produces hallucinations doses of 30 mg or more, far above the therapeutic level will produce coma.

Clinical usage

It is of interest that this well-studied drug has had little use in cardiac therapy until recently and many standard cardiac texts do not mention atropine. The drug is often dramatically effective in treating patients with acute bradycardia and an associated low cardiac output. This situation is often a transitory event following an acute posterior wall myocardial infarction Several mechanisms for such bradycardia have been postulated (1) anoxia of the sino-atrial node with subsequent slowing or arrest and activation of coronary sinus or A-V junctional pacemakers (2) increased parasympathetic tone secondary to neurogenic reflexes or central nervous system disease (3) markedly diminished sympathetic tone (low catecholamine levels have been observed in some such patients)

and (4) administration of drugs such as morphine and digitalis which are vagotonic.

Often hypotension and shock may be associated with marked sinus bradycardia. Occasionally, slow coronary sinus or A-V junctional rhythm develops. Rapid intravenous administration of atropine in 0.4 to 2 mg doses with elevation of the legs is indicated in these patients. The drug can be repeated at intervals of 2 to 3 hours as needed. Not only does the heart rate rise but stroke volume is maintained so that cardiac output may be much improved. In hypotensive patients, there is frequently a return to normotensive levels. Since atropine is often effective in reversing bradycardia, pacemaker insertion or isoproterenol therapy may be avoided. Atropine is not only simpler but at comparable rates may improve cardiac output more adequately than ventricular pacing since the atrial contribution to cardiac output is maintained. Isoproterenol, which may accelerate the heart rate, has several disadvantages. This drug increases myocardial irritability and increases myocardial O_2 consumption unnecessarily. Patients having frequent ectopic ventricular beats associated with bradycardia may, with atropine, accelerate the sinus rate thereby suppressing the ectopic beats without the need for lidocaine or similar antiarrhythmic agents.

Patients with atrial fibrillation and a slow ventricular response secondary to intrinsic A-V nodal disease or digitalis toxicity may also benefit from atropine therapy, although the effects are often not dramatic.

In patients with second degree heart block, atropine effects are variable. The degree of block may decrease, increase, or remain unchanged with parallel alterations in heart rate. Increasing the atrial rate may cause an increase in A-V block as a result of concealed conduction with a subsequent decrease in the ventricular rate. Thus, in patients with bradycardia and second degree heart block, isoproterenol or pacemaker therapy is usually preferable to atropine. In patients with complete heart block and idioventricular or A-V junctional rhythm, the ventricular rate may increase with intravenous atropine, although transient initial slowing may occur. The effect

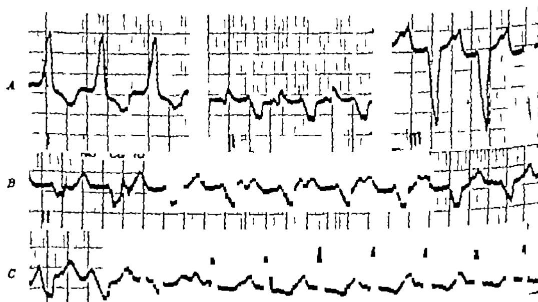


Fig. 1. *A*, Slow idioventricular pacemaker with retrograde P waves. *B*, Thirty seconds following 1 mg of intravenous atropine there is atrioventricular dissociation. The retrograde P waves are now blocked by the more rapid sinus rate. *C*, Beat 3 is a ventricular fusion beat. Then sinus tachycardia follows with a normal appearing QRS complex.

is usually temporary and for adequate long term control pacemaker therapy is necessary

Atropine may occasionally be helpful in clarifying a complex arrhythmia. In Fig 1 a relatively slow idioventricular rhythm was present. Thirty seconds after the intra venous administration of 1 mg of atropine the sinus rate accelerated and produced a transient sinus tachycardia which suppressed the ventricular pacemaker

Atropine has also been suggested as a diagnostic aid in patients who have both coronary artery and acute gall bladder disease. In this group of patients, S-T and T wave abnormalities secondary to gall bladder disease, were reversed with 2 mg of atropine. Electrocardiographic abnormalities due to cardiac disease were not effected The drug has also been suggested as a simple and safe aid in differentiating hypertrophic subaortic stenosis from valvular aortic stenosis.

Summary

Atropine is useful in treating acutely ill patients when bradycardia is associated with a low cardiac output or ventricular irritability Proper administration may avert the need for pacemaker isoproterenol, or lidocaine therapy The drug may also be of diagnostic aid in specific cardiac conditions.

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Further considerations in the design of a highly corrected Z lead*

In a previous report from this laboratory[1] we described a grid-type of Z lead with highly desirable intrinsic properties. As judged by its behavior in an electrolyte filled model of the human torso, this lead responds almost exclusively to the anteroposterior component of dipole moment with only minor sensitivity to the quadripolar and octapolar components of the equivalent cardiac generator. The favorable characteristics of this lead have subsequently been confirmed by a somewhat different kind of model study in another laboratory.

The basic structure of the lead follows McFee and Johnston's proposal that multiple electrodes be arranged in the form of an anterior and posterior grid. In our design each grid consists of 16 electrodes in a square four-by-four array with a spacing of 2.5 inches (6.35 cm.) between individual rows and columns. The two grids are located on the body surface so that their respective centers lie directly in front of and directly behind the centroid of the ventricular mass. The elements of the posterior array are joined together through identical resistors to form an equally weighted Z-plus terminal. In contrast, the Z-minus terminal is formed by a resistor network which sums the anterior electrode potentials in unequal proportions.

The reason for individually weighting the elements of the anterior grid is to synthesize numerous electrodes into an electrocardiographic connection with ideal or nearly ideal recording properties. Our earlier treatment of this interesting and challenging problem of lead optimization led to the previously recommended set of weighting resistors. We have recently returned to this same problem, using a more rigorous type of numerical analysis. The purpose of the present communication is to report the results obtained by the iterative method of treatment and to reinterpret the earlier conclusions in the light of this new information.

The parameters, b_i, of a composite lead may be expressed as $b_i = \sum a_{ij} w_j$ where a_{ij} is the ith parameter of the "jth" electrode, and w_j is the weighting factor which is applied to that electrode. One major objective of compounding is to determine a set of weighting factors such that parameters b_1 through b_{15}, which represent quadripole- and octapole-sensing components of the lead, vanish. The remaining major objective is that the lead vector of the synthesized connection, as specified by its component b_1 through b_3, be collinear with the normal anatomical axis of the lead.

As applied to our torso model data, the relationship given above in the form of subscripted symbols amounts to an underdetermined set of 15 simultaneous linear equations from which 16 weighting factors are to be determined. In this circumstance it might seem attractive to reduce the set to an exactly solvable form by weighting one of the electrodes at zero (thus removing it from the grid array) or at some other arbitrarily selected value. This approach was attempted and then discarded because it produced some negative weighting values, which increase the complexity of the resistor network and tend to attenuate the sensitivity of the lead. The problem of negative coefficients was subsequently handled by adding to the set 16 equations of positive constraint, which were simply $w_1 = 1 \ldots w_{16} = 1$. The least-squares solution of this now overdetermined set of equations resulted in the synthesis of a highly corrected Z lead from simple weighting of the anterior electrodes by purely passive resistance elements.

We have recently succeeded in solving the original underdetermined set of equations, using the method of quadratic programming described by Wolfe to insure the desired non-negativity of all weighting coefficients. The lead parameters of the newly revised connection are given in Table I and the relative values of the weighting resistors in Table II. In both tables, the previously published values appear in parentheses directly below each corresponding new value in order to facilitate comparison of the two sets of results. It is interesting to note in Table I that the new coefficients for lead composition produce only slight improvement of intrinsic properties, and that this minor gain in quality is achieved (cf. Table II) through the removal of electrodes 1, 4, 6, and 9 from the anterior grid.

Despite the inherent superiority of quadratic programming as a means of suppressing non-negative solution values, it does not necessarily follow that the previously described set of weighting resistors

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Table I Intrinsic parameters of a highly corrected Z-lead connection

Generating component sensed		Root mean-square values of individual coefficients							Relative I mped coef
		$\bar{p}_{n0}$	$\bar{p}_{n1}$	q	$\bar{p}_{n2}$	$\bar{q}_{n2}$	$\bar{p}_{n3}$	q_{n3}	
		0 838	−5 248	−0 007					1 000
Dipole	1	(0 827)	(−5 227)	(0 000)					(1 000)
		−0 003	0 053	0 021	0 032	0 013			0 013
Quadripole	2	(−0 010)	(0 077)	(−0 033)	(0 036)	(−0 010)			(0 018)
		0 029	0 020	−0 001	−0 031	0 029	−0 056	0 004	0 015
Octapole	3	(0 029)	(0 027)	(−0 010)	(−0 048)	(0 043)	(−0 060)	(0 012)	(0 019)

Legend. Parameters of the highly corrected lead are given in the form of root-mean square normalized lead field coefficients, $\bar{p}_{nm}$ and $\bar{q}_{nm}$. The values given in parentheses are repeated from the original study[1] for purposes of comparison with values recently obtained by a more rigorous method of numerical analysis. The values in the first row, taken from left to right, correspond, respectively to lead parameters b_1 through b_3 referred to in the text; those in the second row to b_4 through b_8; and those in the third row to b_9 through b_{15}.

should be abandoned in favor of the new set. First, the quality of the lead is not appreciably enhanced by use of the new set of weighting factors. Second, because four of the 16 anterior electrodes are eliminated from the array, the net effect of any error in the placing or weighting of an individual electrode would probably be exaggerated. Stated in somewhat different way since we do not yet know how well lead quality can be preserved in dealing with a variety of torsos, our present preference is for a method which leans heavily on preconceived and easily reproduced conditions of lead construction, such as a very simple basic pattern of electrode application and use of the arbitrary (but highly effective) equations of positive constraint. At the same time, however, optimization by quadratic programming provides for purposes of comparison a measure of the maximum lead quality that can be achieved in any given individual situation.

Table II Individual weighting resistors for grid electrodes

∞	7 6	17 9	∞
(14 4R)	(11 5)	(13 5)	(164 4)
8 7	∞	13 2	13 2
(11 4)	(43 0)	(15 1)	(15 4)
∞	10 7	114 2	36 5
(13 0)	(13 6)	(98 1)	(25 7)
9 8	10 6	30 1	8 1
(12 7)	(12 8)	(14 4)	(10 5)

Legend. The resistor values are shown in positions which correspond to the electrode locations as seen when the torso is viewed in its anterior aspect. The numbering system of electrodes employed in the text is sequential from the reader's left to right and row by row, beginning with the upper row. The resistance values given in parentheses are repeated from the original study[1] for purposes of comparison. Each value presented in the table is to be multiplied by some base resistance, R, such as 10,000 ohms. Note that the elimination of four electrodes from the new set (resistor values of ∞) does not appear to depend upon whether they had been lightly or heavily weighted in the previous arrangement.

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Legal aspects of human organ transplantation

What are the legal problems involved in human organ transplantation? In general, they are related to live donors, cadavers, recipients, attending physicians, and next of kin. For instance, in the case of a gift of an organ inter vivos: In what circumstances may a volunteer donor be considered free from undue influence? Is it legal to mutilate a healthy donor for the advantage of another person? Should the donation of organs or parts of the body be limited to those that could not produce a permanent deficiency in the donor? Should the donor be allowed to consent to a serious operation upon himself for the benefit of another, especially when, as a result of the removal of the donated organ, his health might be seriously endangered with only the prospect of a moderate prolongation of the receiver's life?[27-29] Should the State intervene in such cases? What type of special protection should be given to minors, people of low intelligence, or prisoners in regard to donations of organs or tissues?[22]

Should death be defined and, in this connection, for how long should "life" be maintained in a donor with irrevocable damage to the brain? When does death occur if such "life" is artificially maintained?

Should payment or indemnification be received by the donor or his heirs for his organs? More generally, should human organs or tissues be available for sale? If it is legal to sell organs, must the amount of money paid to the donor be included in his income tax or is it a capital gain? Is the sale subject to sales tax? If the organ is given by the donor to the recipient, should a gift tax be paid? Finally, should the value of usable organs from cadavers be included in the decedent's estate?

What are the standards to be applied to the recipient's consent to transplant? Is it suicide if the intended recipient of a transplant refuses to be operated upon?[28] Should parents or guardians have the right to refuse treatment to their children?

Should a surgeon be allowed to take an organ out of a cadaver without the deceased family's permission in order to save a life? What can or cannot be removed from a cadaver and who can give legal permission? Are testamentary bequests binding on the heirs or next of kin?

Which state or provincial law applies in determining who controls the body of a deceased person? What type of regulations are necessary to control the interstate or interprovincial shipment of organs? Should penalties be provided for wrongful removal of organs from a live donor or from a cadaver?

Has a dead body "human" rights to be protected? What would be the liability of a surgeon who lost a patient, the recipient, owing to his ignorance of the very latest developments in regard to compatibility or some other aspect of transplantation?[28, 29]

Advances in resuscitation and techniques for bypassing the heart and reducing the body's oxygen require a revision of present ideas on the diagnosis of death. The question that arises is whether a vital organ can be removed from a person who still has a heartbeat and a circulation and who according to the traditional standards is "alive," although he is a "living cadaver" because irreversible destruction of brain matter with no possibility of regaining consciousness has taken place.

There is an additional issue as to whether and at what stage, without incurring the danger of a possible charge of homicide, a physician may turn off the respirator or other machine and wait for the heartbeat of a patient to stop so that he is dead according to the conventional definition of death and it is permissible to remove some of his organs. Discontinuation of extraordinary measures to keep a patient alive may perhaps be morally justifiable, but under the classical definition of death still adhered to in many states or provinces, an irreversibly unconscious person whose life depends on a machine is "alive," and until death occurs, it is forbidden to interfere with his body.

The conclusion that a person is dead, who has been kept alive by artificial means, should be based on proof of the existence of irreversible lesions inconsistent with survival, especially the destructive and irreversible character of changes in the central nervous system considered as a whole.

The classical signs of death must be re-examined by the medical and legal professions and brought up to date for purposes of transplantation. However, death does not lend itself to a purely legal definition. It is essentially a technical medical problem. The law must allow physicians to decide the moment of death on the basis of medical evidence. What is needed is a medical definition of death or medical tests that would have legal force.

However, the law should devise certain procedures designed to protect the patient's life against the danger of a hasty diagnosis. For instance, the death certificate of a patient kept "alive" by artificial means should be issued only after consultation with at least two or three physicians. If a transplant is envisaged, the team performing the operation should

not be involved in the ascertainment of the death of the donor. It should only proceed after a decision has been reached as to death and the machines have been turned off by the attending physician upon the advice of one or two other physicians including at least one or two specialists. The members of the transplant team naturally interested in saving their patient should not be placed in a position of conflict of interest. Conversely the medical team working to save the donor's life should not be the same as the one looking after the intended recipient of the transplant.

In the case of a heart transplant and whatever the definition or test of death that is adopted, it is obvious that the donor must be dead before his unpaired organ can be removed. Cadavers are by far the most important source of transplants, since very few organs or tissue may be given by a live donor without endangering his health or his life.

Organs such as the heart, kidneys, and the liver must be removed from the cadaver-donor as soon after death as possible if irreversible damage to the organ is to be avoided. This emphasizes the importance of an immediately available consent.

The basic principle of the common law is that there can be no property in the dead body of a *human being*.[24,25] The person having charge of a body cannot be considered the owner of it; he holds it only as a trust for the benefit of those who may from family relationship or friendship have an interest in it.[26] At common law an heir has no property right in the body of his ancestor.[27] Conversely a person cannot by will or otherwise dispose of his body after death and any directions he may have given are not binding upon his personal representatives or survivors.[28]

In general, in the absence of testamentary disposition providing otherwise, the right to the possession of a dead body for the purposes of preservation and burial belongs to the surviving spouse, children, and next of kin. Where the deceased person has made a will naming one or more executors, this right to possession would appear to be vested in the executor or executors.

At common law permission for the removal of organs or tissues from the body of the deceased must be granted by the person or persons who are lawfully in possession of the body for the purpose of burial. Since organs must be removed as soon as practicable after death it is often impossible to locate the lawful possessors in time in order to obtain their authorization. Should removal take place without such authorization, the members of the transplantation team would be civilly and criminally responsible. For instance an action for damages will lie at common law for the negligent handling of a cadaver or interference with its possession on the basis of the mental distress without circumstances of aggravation suffered by the spouse or the next of kin as a result of the wrongful act. No actual pecuniary damages need be alleged or proved. Statutory offences have also been created in relation to the removal of dead bodies or parts thereof.

In many states or provinces there are human tissue acts that provide for the use of dead bodies "for therapeutic purposes or medical education or research in accordance with the request of the donor."

Some of these acts, as for instance the Ontario Human Tissue Act,[29] do not change the common law rule that the deceased's wishes are not legally binding *upon his representatives or survivors*, since in cases where the deceased had made a request in the prescribed manner that his body or a specified part or parts thereof be used after his death for the purposes mentioned above, a specified person may not authorize the use of the body or the removal of the part or parts of the body and their use in accordance with the request.

Where the donor dies in a hospital, its administrative head or the person acting in that capacity may authorize the use of the body or parts thereof unless he knows that any of the close relatives object to their use. However if the donor's *whole body* is not required by the hospital, the administrative head of the *hospital shall immediately* notify the local inspector of anatomy who shall then take control of the body. In such a case it would seem that the surviving relatives cannot object to the disposal of the body as the statute uses the word "shall" instead of "may."

When the donor dies in a place other than a hospital, the person who may give permission for the body or any of the parts thereof to be used in *accordance with the wishes of the deceased* is "his spouse or if none, any of his children of full age or if none, either of his parents or if none, any of his brothers or sisters or if none, the person lawfully in possession of his body."

No permission shall be given if the person who made the request subsequently withdrew it. When the deceased has made no request and there is no evidence that he would have objected, whether the donor dies in or outside a hospital, his spouse or if none, any of his children of full age or if none, either of his parents or if none, any of his brothers or sisters or if none, the person lawfully in possession of the body of the deceased person may authorize *the removal of any specified part or parts from the body* of the deceased person by a duly qualified medical practitioner and their use for therapeutic purposes or for the purpose of medical education or research."[30]

In the case of a patient who has not made a request to be a donor [and] is in the opinion of a duly qualified medical practitioner incapable of making such a request and his death is imminent and inevitable, provided there is no evidence that the deceased would have objected, his relatives, taken in the same order as in the preceding case, may authorize the removal after death of any specified part or parts from the body of the person by a duly qualified medical practitioner and their use for therapeutic purposes or for the purposes of medical education and research.

This provision is primarily concerned with the unconscious victim of an accident whose life may be artificially maintained by mechanical devices. In order to insure the maximum success for the transplantation operation the act allows the necessary authorization to be obtained from his relatives before actual death.

The acts or statutes of some provinces[31] or states change the common law and enable a person of eighteen years of age or over in writing at any time or orally in the presence of at least two witnesses

during his last illness, to direct that his body or any specified part or parts thereof be used after his death for therapeutic purposes or for purposes of medical education or for purposes of medical research.

Upon the death of this person, the direction is binding and is full authority for the use of the body or for the removal and use of the specified part or parts thereof for the purposes specified in the direction, except that person shall not act upon a direction if he has reason to believe that the person who gave the direction subsequently withdrew it. In other words the direction is binding on the executor and close relatives and does not depend upon further authorization following the death of the donor. Thus, the wishes of the deceased cannot be defeated.

The difficulty for a hospital is to find out whether the deceased gave a direction or whether he had withdrawn it. It would be advisable for every person in the United States and Canada to carry a card stipulating that he has given such direction, or every voluntary donor could carry a card containing the following information: name, address, age, blood group (certified by a reputable laboratory), histocompatibility, and the words, voluntary donor followed by his signature and that of two witnesses. This would solve the difficulties involved in obtaining prior consent or locating such a consent.

Where person dies who has not made a direction, his spouse or if none, an of his children, etc. may direct that the body or any specified part or parts thereof be used for therapeutic purposes or for purposes of medical education or research unless the deceased, if living would have objected thereto.

Because at present there exist diversity of statutory provisions in the various states of the United States, the National Conference of Commissioners on Uniform State Laws adopted a Uniform Anatomical Gift Act,[a] which deals with gifts of bodies or parts thereof to take effect after death. This act, if enacted widely in the United States, will be of great benefit to the medical profession. The gift may be made by the donor in his lifetime, assuming that he is of sound mind and 18 years of age or more if not made ante mortem, and in the absence of notice of contrary indications by the decedent or actual notice of opposition by a member of his family it may be made by the surviving relatives in a stated order of priority. The gift, which may be executed by document in writing or by will, must be signed and witnessed by two persons. Delivery is not necessary to validity. It may run to a specific donee or to a licensed hospital, teaching institution, or physician, etc.

Provisions are made for revocation during the lifetime of the donor. Of course the gift is binding upon relatives and effective in any state. This act does not deal with the time of death which is to be determined by the attending physician, nor does it cover the question of payments for gifts. Finally there is no attempt to prescribe who shall get the organ if there is a shortage of supply. The physician who certifies the death must not participate in the procedures for removing or transplanting a part.

To conclude, perhaps the best way to solve moral, ethical, and legal problems connected with human transplants is to make available artificial organs to be permanently built into patients.

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Hemodynamic effects of ethyl alcohol in man

Only sporadic reports concerning the hemodynamic effects of ethyl alcohol in man have been published. Some investigations have demonstrated rise in heart rate.[2-4] By means of the ballistocardiogram Horwitz and associates observed no significant change of the cardiac output in man after alcohol. The following is a brief report of a study on the effect of orally given ethyl alcohol on cardiac output, stroke volume, and peripheral resistance in man.

Fourteen healthy male volunteers were given ethanol 0.92-1.91 ml. per kilogram mixed with 350 ml. of juice (flavored water) which they drank within five minutes. The cardiac output, stroke volume, total peripheral resistance, and the blood alcohol levels were measured at regular intervals every 10 minutes up to 140 minutes. We determined the blood alcohol enzymatically with alcohol dehydrogenase and DPN/DPNH as coenzyme. The cardiac output was measured with dye dilution methods. Details of this procedure are described elsewhere.[8] Relating the hemodynamic findings to the blood alcohol levels, subjective factors like different alcohol absorption rates could be eliminated.

With respect to the blood alcohol levels the following results were obtained (Table I). At a blood alcohol level of (average) 39 mg. per cent the cardiac output rose by 6 per cent, at 120 mg. per cent by 18 per cent. The difference of the cardiac output by a blood level of 39 mg. per cent and of 120 mg. per cent is statistically significant ($p < 0.05$). In like manner the heart rate was dependent on the blood ethanol level showing a maximum rise of 13 per cent by 85 mg. per cent ($p < 0.005$). The total peripheral resistance was lower at blood ethanol concentration of 85 and 120 mg. per cent than at 39 mg. per cent ($p < 0.025$). No significant changes were noted in

Table I Means and standard deviations of cardiac output stroke volume heart rate, and peripheral resistance in relation to the blood alcohol levels

Blood alcohol (mg %)	Blood alcohol (average—mg %)	Cardiac output (L./min.)	Stroke volume (ml.)	Heart rate	Peripheral resistance (dynes×sec.×cm.
0		6 01 ± 0 3	83 ± 4 3	74 ± 2 9	1 396 ± 83
<50	39	6 39 ± 0 4	83 ± 5 1	77 ± 2 9	1 370 ± 95
51 to 75	65	6 30 ± 0 4	82 ± 6 0	79 ± 3 5	1 413 ± 78
76 to 100	85	6 42 ± 0 4	79 ± 5 4	82 ± 4 6	1 311 ± 88
>100	120	7 00 ± 0 5	90 ± 17 3	82 ± 10 8	1 185 ± 114

the stroke volume accordingly the increased cardiac output was directly related t the rise in heart rate

As the fluid intake may have an effect on the hemodynamics w dditionally measured the circulatory parameters of seven subjects who received 350 ml. of juice, and compared the results with those of seven subjects, who drank the same amount of juice with alcohol. The blood alcohol levels after 10, 20, and 40 minutes were on the average 38, 60 and 67 mg per cent The heart rate increased after alcohol by 12 8, and 13 per cent. The corresponding changes after j ice wer +1 0 and +6 per cent. The difference of the heart rates after ethanol and juice is statistically significant ($p < 0.05$). The cardiac output ose after alcohol within 10 minutes on the average by 14 per cent, but did not change after juice The difference is significant ($p = 0.05$). Forty minutes after 350 ml. of juice a rise in cardiac output of 10 per cent was seen The total peripheral resistance increased slightly 10 minutes after 350 ml. of juice, but was reduced after ethanol and dropped by 9 per cent 30 min tes later

Cook and Brown demonstrated a rise of the blood flow in the hands, concluding an elevation of the cardiac output after ethanol. Using an electromagnetic flowmeter Webb and Degerli[16] observed on anesthetized dogs, given 0.5 Gm. of ethyl alcohol per kilogram, a slight rise in heart rate and a significant increase in cardiac output and stroke volume, while the peripheral resistance fell moder tely With higher doses of alcohol (1.5 Gm per kilogram of body weight), the total peripheral resistance fell significantly and a rise in pulse rate was no longer demonstrable Similarly our subjects with a blood alcohol above 100 mg per cent showed no further increase of the heart rate in comparison with lower alcohol levels. There was a noticeable decrease of the peripheral resistance with a significant rise in cardiac output. Ganz[12] observed in anesthetized dogs decrease in cardiac output and a considerable rise in the peripheral resistance with unchanged blood pressures and pulse rates after ethanol. These findings are contrary to our results and to those of other authors.[14-16] One reason might be the different mode of alcohol application, as the animals in the series of Ganz received the alcohol intravenously at a concentration of 96 per cent. Schmitthenner and associates noted an increase of cardiac output and left ventricular work with an ethanol concentration of 70 to 120 mg per cent. The mean arterial pressures were unchanged.

The dependency on the blood alcohol level for the increase in cardiac output, which is directly related to a rise in heart rate, and a decrease of the total peripheral resistance appear to be the essential circulatory effects of ethyl alcohol in man. In the heart-lung preparation no immediate hemodynamic changes on ethanol were demonstrable.[17] As Massermann and associates[18] observed an increased activity of the hypothalamus after alcohol and Heymans and co-workers[19] reported that ethanol affected the proprioceptive cardiovascular reflexes, we conclude that the alterations of the hemodynamics after alcohol are due t cerebral or central nervous reflex mechanisms.

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Cardiotoxic effects of Mellaril: Conduction disturbances and supraventricular arrhythmias

Thioridazine (Mellaril) is known to cause electrocardiographic repolarization abnormalities and ventricular arrhythmias in patients on oral daily doses of 200 to 1,500 mg.; these abnormalities usually consist of prolonged Q-T intervals, accentuated U waves, isolated T-wave abnormalities, and premature nodal and ventricular contractions followed by ventricular tachycardia. No cases are recorded of conduction disturbances or supraventricular arrhythmias related to Mellaril therapy; however, we have recently seen three patients who developed first degree atrioventricular block with intraventricular conduction delay, nonconducted premature atrial beats, and atrial flutter with variable block while on Mellaril therapy.

Patient S. H., a 35-year-old Caucasian female, was admitted after ingestion of approximately 625 mg. of Mellaril. The admission electrocardiogram (ECG) (Fig. 1) revealed sinus tachycardia of 140 beats per minute, first degree heart block with a P-R interval of 0.20 (the P waves being in the downslope of the preceding T), slightly long Q-T interval (0.32) for the rate, and an intraventricular conduction delay with a QRS interval of 0.16. With general supportive care, the patient subsequently recovered without complications and was discharged from the hospital. Approximately four months later, a follow-up ECG was normal.

Patient G. B., a 46-year-old Mexican woman, was admitted because of syncope. She was on Mellaril, 100 mg. three times daily, and amitriptyline (Elavil) 25 mg. four times daily. The admission ECG revealed sinus bradycardia, premature atrial contractions (conducted and nonconducted), Q-T interval prolongation, and flat T waves. She was taken off Mellaril and discharged with a normal ECG. One year later Patient G. B. was again started on Mellaril, 100 mg. three times daily, and Elavil, 25 mg. twice daily, and was again admitted because of syncope. An ECG (Fig. 2) showed sinus bradycardia, premature ventricular contractions, premature atrial contractions, and a short run of ventricular tachycardia. The Q-T interval was prolonged and the T waves were inverted. All medications were again discontinued, and a repeat ECG (without medications) six weeks after hospital discharge was normal.

Patient J. W., a 51-year-old chronic alcoholic, was admitted with the diagnosis of delirium tremens. He was treated with paraldehyde, Dilantin, phenobarbital, and Mellaril (25 mg. four times daily) and developed a rapid heart rhythm of 160-180 per minute. An ECG (Fig. 3) showed atrial flutter with variable 2:1 block and an average ventricular response of 180 beats per minute. He spontaneously (with nasal oxygen) converted to sinus tachycardia of 120 beats per minute with an otherwise completely normal ECG. Mellaril was discontinued and he was discharged from the medical service two weeks later, at which time an ECG was completely normal.

Thioridazine (Mellaril), a phenothiazine derivative, is a moderately potent tranquilizing agent. Compared to other phenothiazines, it is reported to have few extrapyramidal side effects, and no jaundice or agranulocytosis has been reported with its use. Therefore, it is a frequently prescribed medication, especially in the practice of psychiatry, both in outpatients and in inpatients. In 1963 Kelly and

associates[4] reported abnormal Q-T intervals nd accentuated U waves in 28 patients receiving high doses of oral Mellaril (200 mg or more per day) In this group he suspected runs of complete heart block and ventricular tachycardia in two patients, one receiving 3 600 mg per day and the other 1 500 mg per day none however had any alter tion of the QRS complexes. Several deaths, probably related t ventricular arrhythmias occurred and all had nonspecific trophic changes in the myocard um. Interestingly in the same year Mada and Pendse[4] reported a study of the ntiarrhythmic effects of Mellaril in ten dogs he concluded that the drug was similar t q nidine in its actions was particularly effective in ventricular tachycardia, reduced the duration of atrial fibrillation, and converted atrial flutter

In 1964, Wendkos reported 50 male psychiatric patients who were all on 600 mg or more per day of Mellaril; in these patients he recorded labeled T wave changes which he felt reverted to near normal by the adm istration of potassium chloride In this same year Ban and St Jean[4] reported the electrocardiographic analyses of 18 patients on phenothiazines (six each on Mellaril, chlorpromazine nd Stelazine). H found that all six receiving Mellaril had increased Q-T intervals ith T and U wave changes only three of six patient receiving chlorpromazine had such changes, and only two of six on Stelazine had changes. In addition, Schroe-

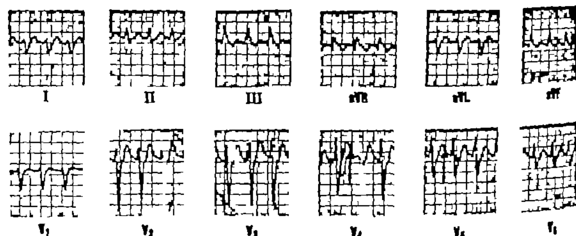


Fig 1 Admission ECG on Patient S. H. which shows sinus tachycardia of 140 beats per minute, a first degree heart block with P R interval of 0.20 (the P waves are in the downslope of the preceding T re— see arrows) a slightly long Q-T interval for the rate (0 32), and an intraventricular conduction delay with QRS interval of 0.16.

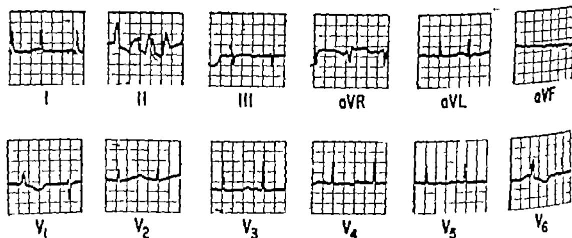


Fig 2 Second admission ECG on Patient G B. showing sinu bradycardia, prolonged Q-T interval, inverted T waves, premature atrial beats, premature ventricular beats, and a short run of ventricular tachycardia (Lead II).

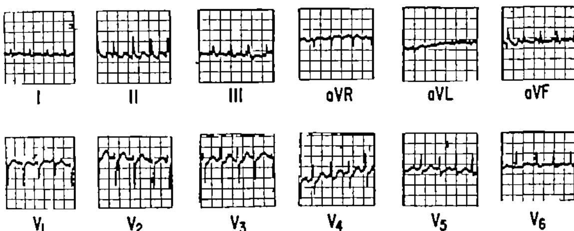


Fig. 3. Initial tracing on P tient J W showing atrial flutter with variable block and ventricular response of 160 beats per minute.

maker and associates[2] described patient receiving 600 mg of Mellaril per day who had prolonged Q-T interval and subsequently developed premature nodal and ventricular contractions finally followed by ventricular tachycardia the patient responded poorly to drugs, but was treated successfully with artificial pacing

Alexander and associates, in 1967 reported pigment changes in the myocardium and changes in the arterioles of patients who had died of phenothiazine overdosage. All of these patients had electrocardiographic changes represented by blunted and notched T waves, increased Q-T intervals, U aves, and elevated S-T segments. He also reported ten schizophrenic patients (without evidence of heart disease), of hom five were treated with Mellaril (600 to 1 000 mg per day) and five with placebo Electrocardiographic changes were noted in the treated group hen the daily dose of Mellaril reached 300 mg These changes consisted of flat, broad T w es nd increased Q-T intervals no arrhythmias, no conduction abnormalities, and no abnormal myocardial function ere noted. The placebo control group had no electrocardiographic changes. N effect on the electrocardiographic changes or the serum enzymes was noted when the patients were given supplementary potassium.

I early 1968 Giles nd Modlin reported tw patients on Mellaril who died as result of ventricular arrhythmias and t autopsy had evidence of myocardial atrophy with fragmented cytoplasm in many cells. Later Burda described 12 year-old boy ho had ingested pproximately 4,000 mg of Mellaril. The T waves were flattened, broadened, notched, and inverted, and the Q-T interval was slightly prolonged. This patient survived, and the ECG returned t normal in four days.

Of our three patients discussed herein, two developed electrocardiographic changes heretofore not previously described in association with Mellaril these were first degree trioventricular block ith intraventricular conduction delay and atrial flutter ith variable block. The findings in Patient G B are significant in that on tw different occasions, the electrocardiographic changes and the arrhythmia resolved when Mellaril was discontinued, further erifying the distinct association of Mellaril with the changes described The reason for these electrocardiographic changes in our patients is unknown. However it could be postulated that in Patient S H depression of conduction was due to Mellaril since Madan and Pendse[4] have shown this phenomenon t occur experimentally in dogs.

The conduction disturbances and supraventricular arrhythmia reported here constitute new and linically significant cardiac complications associated with Mellaril therapy Although the precise cause nd effect relationship is not well defined, the association of these electrocardiographic abnormalities with Mellaril seems to be much greater than one would expect from chance alone. For this reason, it is felt that any patient on Mellaril should be observed closely for such problems and that, in patients with significant heart disease, Mellaril should be employed only with great caution.

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Letters to the Editor

Cardiac causalgia

To the Editor

I would like t take issue with the editorial, "Cardiac Causalgia, by Drs. Burch, Phillips, and DePasquale (AM. HEART J 76 725, 1968). My first point is to dispute the authors designation cardiac causalgia for the phenomena observed. Although it is difficult to criticize because no reference to case histories is given, and because the term causalgia has been so loosely used throughout medical literature, there seem to be several elements missing from the "traditional" concept of causalgia[1-5] (1) regional changes in sensibility of the painful area which include hyperesthesia and hypesthesia often in different zones[1] (2) temporary relief by measures such as application of moisture over large area or by the use of warm or cool applications[1] (3) exaggeration of pain by emotional stimuli[1] (4) relief of pain by sympathectomy

While it may be true, as the authors speculate, that visceral causalgia exists and accounts for the absence of these characteristics (which have been described in extremity causalgia), there is still need for explanation of these differences.

My second point is that the editorial does not include the authors observations regarding emotional factor in the etiology of the pain and also depreciates others observations that personality components and emotional states are involved. They even reveal a distinction between "genuine and nongenuine pain which is an untenable concept of pain.

Localized pain as result of psychological processes is ell documented in the literature [6-11] Conversion reactions with pain[6,11] and depression ith pain are the most frequent examples. Furthermore, pain arising from the chest wall, perhaps the most common form of chest pain seen by the physician, is closely related t the psychological tate of the patient Certainly the group of patients who have formed the clinical material for the editors observations are prime candidates for unresolved psychological stress.

I hope that f rther tudy of chest pain in such patients will clarify the sources of the symptoms Pseudoexplanations may be the stimulus for further observations

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What death is like

To the Editor

In the annotation entitled "What Death I Like (September 1968), the authors conclude that "*biologic death* is not an unpleasant experience but only deep eternal sleep.

It is very interesting to note that similar statements were made by Plato 2,500 years ago. I his great Socratic dialogue on the trial and condemnation of Socrates, the philosopher notes

Let us reflect in another ay and we shall see that there is great reason to hope that death is good for one of two things—either death is state of nothingness and utter unconsciousness, or as men say there is change and migration of the soul from this world t another Now if you suppose that there is no consciousness, but sleep like the sleep of him

who is undisturbed even by dreams, death will be an unspeakable gain. For if a person were to select the night in which his sleep was undisturbed even by dreams, and were to compare with this the other days and nights of his life, and then were to tell us how many days and nights he had passed in the course of his life better and more pleasantly than this one, I think that any man, I will not say a private man, but even the great king will not find many such days or nights, when compared with the others.

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*Plato. Apology. The Four Socratic Dialogues of Plato, trans. Benjamin Jowett. Oxford, 1949, Clarendon Press, 97.

Is the spectral absorption of indocyanine green altered by radiation?

To the Editor:

Cardiac output is of interest in radiation studies of the cardiovascular system. Since cardiac output is commonly determined by the dye dilution technique using indocyanine green as the dye, any alteration in the light absorption characteristics of this dye would produce erroneous values in cardiac output determinations. The absorption spectral characteristics of indocyanine green have been reported to be altered by reducing substances as well as by oxidizing agents such as hydrogen peroxide. Since the irradiation of water, a major component of cells and body fluid, produces reactive radicals and peroxides including hydrogen peroxide, a study was undertaken to determine if radiation significantly alters the absorption characteristics of indocyanine green. Furthermore, since neutrons activate blood sodium, the dye injected into an animal irradiated with neutrons is subjected to an environment of radioactive sodium.

In the first experiment, blood, freshly drawn from male beagles and made anticoagulative with heparin, was placed in glass test tubes. Five tubes of blood and five tubes of an aqueous solution of indocyanine green of standard injectable concentration (5 mg. per milliliter) were placed in the reactor exposure room with the distances from the reactor core varied to obtain the desired mixed gamma-neutron doses. The samples were irradiated using a $1.00 pulse. The dose to each sample was monitored with a sulfur pellet; however, the reported doses are based on the tissue kerma,* free-in-air, determined as a function of room position and integrated reactor power with paired (tissue equivalent and graphite-CO_2) ionization chambers. The absorbed dose reported was considered to be equal numerically to the tissue kerma; a more accurate determination of the absorbed dose was considered unnecessary for this experiment. The following doses were recorded: 0.55, 1.0, 5.5, 21 and 48 kilorads. The irradiated blood samples were diluted 1:10 using normal saline, and unirradiated or irradiated indocyanine green solution was added so the ratio of diluted blood to dye solution was 3,000:1. (This dilution was previously determined to be a satisfactory ratio for recording the absorption spectrum.) Ten control samples containing unirradiated blood and dye was used. Each reference blank was identical to the corresponding sample except no indocyanine green was added. Cuvette volume was 3.0 ml. in all cases. The optical density of each sample was measured from 700 to 850 nm using a spectrophotometer (Cary 14 Recording Spectrophotometer).

In a second experiment, blood was obtained from two dogs 1.5 hours following irradiation. One dog received 5,000 and the other 10,000 rad whole body doses of mixed gamma-neutron radiation. Blood was diluted, unirradiated indocyanine green added, and absorption of the samples measured over the range of 700 to 850 nm.

The absorption peak of the control absorption spectrum (unirradiated blood and dye) occurred at 803 nm. The spectra of all the irradiated samples from experiments one and two had absorption peaks identical to the controls, and the heights of the peaks were not significantly different from those of the control.

These findings demonstrate that indocyanine green may be used for cardiac output determinations in animals containing radioactive materials. Neither the absorption spectrum nor the absorptivity of injectable solutions (5 mg. per milliliter) of indocyanine green was significantly altered by large doses of mixed gamma-neutron radiations. In a separate experiment, not reported here, the absorptivity of very dilute aqueous solutions of dye (11 µg per milliliter) was decreased from 15 per cent following 500 rads to over 90 per cent after 20,000 rads. However, such dilute solutions of indocyanine green would not be used in routine cardiac output determinations, and standard solutions of dye were not significantly altered by radiation.

In addition, indocyanine green has other characteristics that make it especially useful as a dye for cardiac output determinations. The most important characteristic is peak light absorption in blood at 805 nm, which is the point where oxyhemoglobin and

*Kerma = kinetic energy released in material, a quantity which represents the kinetic energy transferred to charged particles by the uncharged particles per unit mass of the irradiated medium. This is the same as one of the common interpretations of the concept "first collision dose," that has proved to be of great value in the dosimetry of fast neutrons. (Ref.: Radiation quantities and units. International Commission on Radiological Units and Measurements (ICRU) Report 10a, National Bureau of Standards, Handbook 84, 1962.)

reduced hemoglobin absorb light equally (isosbestic point). Thus, changes in the degrees of oxygenation of the blood do not affect the amount of light absorbed. Blood changes such as variations in pH plasma protein, and electrolyte concentration do not affect the absorption characteristics of this dye. These are changes which might occur in irradiated animals.

We express our appreciation to W. Pfeiffer for conducting the dosimetry measurements, G. Catravas for use of the spectrophotometer, and Dr. H. Dunning of Westcott & Dunning for supplying the indocyanine green.

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Book reviews

THE GEOGRAPHIC PATHOLOGY OF ATHEROSCLEROSIS Edited by Henry C McGill, Jr M D Baltimore, 1968, The Williams & Wilkins Company 653 pages. Price $8.25

This book on geographic pathology of atherosclerosis ummarizes some of the concepts of the selected contributors. Most of the data are concerned with epidemiologic pathology Several of the authors have been concerned with quantitating the pathology of atherosclerosis, most difficult if not impossible task. Regardless of one opinion of their success in this regard, the book does summarize their data. From the point of view of the clinician factors other than quantity are important, e g site and vulnerability with respect to site and extent of the lesion A single lesion in the wrong place can be more serious than many lesions elsewhere.

Techniques of study tatistical methods, and types of lesions and some of the consequences are discussed. Several epidemiologists are contributors. Such factors as age, sex, race, obesity diet, geographic location, dietary habits and customs, diabetes mellitus, and hypertension are discussed. The cardiologists and pathologists who have followed the world literature for many years will be pleased to have the tables and charts and other data available but will find little really new data. In fact, many of the factors have been known since the early part of the century Nevertheless, McGill has brought together a summary of recent studies for the many physicians and pathologists who have not followed the literature closely Furthermore, it is convenient to have these data readily available in a single volume.

This is a useful book for students and others in postdoctoral training Unfortunately the references only rarely include publications in the third and fourth decades or earlier of this century For example, not one of the studies of Winternitz is included. Therefore, those who are interested in learning the advances being made in the field of the pathology of therosclerosis will need to search the literature more carefully Nevertheless, from the point of view of strictly geographic pathology of recent times, the monograph can fulfill a useful purpose.

PATHOLOGY OF THE HEART AND BLOOD VESSELS. Edited by S. E. Gould, M D D.Sc., Springfield, Ill., 1968 Charles C Thomas, Publisher 1198 pages. Price $42.50.

This textbook has served an important function in cardiology The third edition is welcomed. Gould has gathered excellent contributors who have made possible a useful book on pathology of the heart and blood vessels. The field is as thoroughly presented as could be expected in a single volume. The text is clearly written and the illustrations numerous and clear Obviously many details are lacking in a book of little over a thousand pages so that those who are concerned with detailed aspects of pathology will need to resort to the medical literature. The bibliography appended to each chapter provides well-chosen references for supplemental *information*. This is a very good textbook.

COMPUTING IN MEDICINE. Edited by C. C. Spicer British Medical Bulletin, vol. 24 no. 1, London, September 1968.

The symposia of the British Medical Bulletin have been consistently excellent. Not only have the subjects been timely but the contributors well selected. This is true for the present number. The use of computers in medicine has just begun. Their use will continue to increase as computer science advances. This issue of the Bulletin includes such topics as technology vocabulary, preparation of clinical data for computer linkage of medical records, and use in diagnosis, radiobiology radiotherapy neurological diagnosis, and chromosome analysis. This issue is of considerable importance to all specialties of the medical profession, including of course those in computer science.

PAEDIATRIC CARDIOLOGY Edited by Hamish Watson, St. Louis, 1968, The C V Mosby Company 996 pages. Price $36.50.

Hamish Watson has edited a very good textbook of pediatric cardiology The a thor trained as an internist, became interested in pediatric cardiology because of the activities in cardiac catheterization. He is an outstanding pediatric cardiologist who has gathered internationally prominent pediatric cardiologists as contributors. The textbook includes expected aspects of pediatric cardiology, i.e., embryology anatomy fetal circulation, malformations, phonocardiography, roentgenology, catheterization, and specific diseases and congenital defects. Each disease is presented in essentially the conventional textbook manner The illustrations are numerous, clear and well described and labelled. The bibliographies appended to each chapter are usef l. This is textbook for students and physicians, not only pediatric cardiologists. The book, expensive as all books today is recommended to all in the practice of cardiology pediatric, and internal medicine.

CLINICAL MANAGEMENT OF SHOCK SURGICAL AND MEDICAL. By Robert M Hardaway III Springfield, Ill., 1968, Charles C Thomas, Publisher 599 pages. Price $22 00.

Hardaway book, *Clinical Management of Shock* is welcome in this time of war A book of this type is useful in view of the problems in cardiogenic shock. Surely no one can define shock satisfac torily Nevertheless, the well-trained clinician has no difficulty in recognizing it. The book is written for the physician and the surgeon. Wisely in a book of this nature Hardaway refrained from discussing in great detail the theories of the mechanism of shock. In fact he discusses theories in four pages only

Readers will differ in opinion with the author For example there are some ambiguous or vague statements, such as on page 13 "The expanded vascular space should be adequately filled. This statement leads the eader to assume that part of the vascular bed is empty This statement could be improved upon since the blood vessels are always full. The volume of the vascular system and the volume of blood within are always equal, even in shock.

The discussions on pathologic physiology in travascular clotting, the shock unit t the Walter Reed Hospital and in Vietnam, as well as the treatment used, are good. The illustrations are clear The index and bibliography are very useful, including the appendix on equipment for shock unit and costs. This is a very good practical book on most important subject. The book is highly recommended.

CONGENITAL ANOMALIES OF THE CAROTID ARTERIES. By T A. Lie, Excerpta Medica Foundation, Baltimore, 1968 The Williams & Wilkins Company 143 pages. Price $10.00.

This is an extremely important book in view of the increasing interest in cerebral angiography and surgery on the cervical and cerebral arteries. Unless the physician concerned knows thoroughly the nature and incidence of anomalies of these vessels, serious errors in judgment can follow to the detriment of the patient. Lie has reviewed the literature very well and has included clear angiograms. The anomalies are nicely integrated into the clinical manifestations. The chapters include embryology congenital anomalies of the carotid arteries and of the basilar and vertebral arteries, and their anastomoses. This is a very important, useful, clearly written, and concise book of only a few pages.

CARDIAC DIAGNOSIS. By Noble O Fowler M D New York, 1968 *Paul B. Hoeber Inc., Medical* Division, Harper & Row Publishers, 722 pages. Price $23.50.

Fowler and his associates from the University of Cincinnati Medical School with the assistance of Franch of Emory Medical School have produced a new book on cardiac diagnosis. This aspect of any disease is most important. The authors of the various chapters have selected aspects of diagnosis that would be of interest to practicing cardiologists as well as to those in training in general medicine and cardiology The book is good one It is well organized and supported by good illustrations, bibliography nd index. Some aspects of the book impress this reviewer however For example, it does not include a chapter on history taking, one of the most important aspects in diagnosis of any type of heart disease. Fowler also has not included a chapter on or discussion of the general examination. These deletions may have been intentional since he seems to have written the book more for well-established cardiologists and internists. Nevertheless, there are important aspects of chest pain, for example, which are related to cardiac diagnosis that require general consideration since patients consult physicians because of pain which may or may not reflect ischemic heart disease, pericarditis, aortitis, aortic aneurysms, or noncardiac states. T include a chapter on vectorcardiography is understandable but not to the exclusion of chapter concerning the general aspects of history taking and the physical examination.

The policy in this book is again reflected in the chapter on myocardial diseases in hich the historical and physical manifestations common to all or most of the cardiomyopathies are only briefly discussed. For example, the reader is not adequately informed that pregnant patients may develop any disease that nonpregnant patient can develop, but that some cardiologists are of the opinion that specific type of cardiomyopathy related to the early postpartum period occurs which is known as postpartum heart disease. The entity may not be common in Cincinnati but it is common in South America, for example, and some parts of the United States

Surely cardiologists have differences of opinion on many aspects of diagnosis of heart disease These differences are evident in the book Nevertheless, Fowler and his associates have produced a good and useful book which should assist beginners as well as practicing physicians in the diagnosis of heart disease.

Announcements

Myocardial Infarction Symposium sponsored by the Cardiopulmonary Institute Methodist Hospital of Dallas, will be held Sept 11 through 13 1969 in Weiss Auditorium, Dallas Texas.

American Institute of Ultrasound in Medicine Fourteenth Annual Conference, sponsored by the American Institute of Ultrasound in Medicine and the Department of Continuing Medical Education University of Manitoba will be held on Oct. 6 through 10 1969 at the Hotel Fort Garry Winnipeg, Manitoba

There will be a 2 day diagnostic workshop with basic principles, intended for those newly acquainted with ultrasound or those wishing a refresher course in the diagnostic applications of ultrasound There will also be a 2½ day scientific session. Scientific papers are to be solicited on the clinical application and developments in technique and instrumentation of diagnostic, therapeutic, and surgical ultrasound.

Four hundred (400) word abstracts, including figures, should be sent by June 30, 1969 to: Ross E. Brown M D Program Chairman, AIUM Department of Continuing Medical Education, 15 Medical College Building, Bannatyne and Emily Streets, Winnipeg 3 Manitoba.

Abstracts will be published as proceedings of the meeting and will be distributed at the meeting

For further information concerning details of this conference write Dr Ross E. Brown at the above address.

American Heart Journal

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Editorial

Myocardial damage secondary to brain lesions

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The last year has seen the development of the new technique of cardiac transplantation. From information in the press, it appears that the donors of the hearts have usually died of cerebrovascular accidents or head injuries. The donors have been young or middle-aged and might be presumed to have had normal hearts up to the time of their terminal illness. However, at least one donor suffered several cardiac arrests before his heart was removed and this is a clear indication of functional heart impairment. It is of importance then to establish whether patients dying of neurological disorders have heart damage of a more serious nature. It is also of importance to such patients themselves as brain damage and cerebral edema will be adversely influenced by any impairment of the circulation.

There are good reasons for thinking that patients with brain lesions may have myocardial damage. Clinical experience in neurosurgical units shows that patients die often unexpectedly of cardiac arrest, arrhythmia, or severe hypotension in the absence of any pre-existing heart lesion or blood loss. It is now also well known that many different forms of intracranial disease may be accompanied by abnormalities in the electrocardiogram (ECG).[1] These changes have been reported from all over the world and in many cases are comparable in degree to those seen in clinical myocardial infarction. But myocardial damage has been found at necropsy in very few cases. Wasserman and associates mention one patient who developed myocardial infarction while in the hospital following a subarachnoid hemorrhage and Burch and his colleagues reported one similar case where the heart was found to have areas of necrosis. In other cases where necropsy findings are reported the hearts showed no recent abnormality even when the ECG had shown changes of infarction.

A recent paper[11] reported increased levels of creatine kinase in the serum of neurosurgical patients. This increase was due to the isoenzyme of muscle and not brain. Since none of the patients had any skeletal muscle damage or wasting, it seems probable that the creatine kinase came from a damaged myocardium.

There is then clinical, electrocardiographic, and biochemical evidence that changes in the heart may accompany intracranial disease.

Experimental work also suggests that the heart may be adversely affected by nervous influences. It was shown in 1937[13] that vagal stimulation in dogs can cause changes in

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the ECG signs of cardiac decompensation and myocardial infarction Other visceral lesions in these dogs were the same as those frequently found in patients dying with brain lesions. Changes in the ECG and cardiac dysfunction have since been reported following stimulation of the hypothalamus and medial temporal lobe structures [12,14] Head injury in mice can produce electrocardiographic changes[15] and intracranial injection of blood can cause heart damage [1] Focal myocardial lesions can also be caused in rabbits by injection of air into the ventricles of the brain [7]

There is thus a paradox. Experimental work suggests that myocardial damage should be one of the visceral effects of brain disorder in man and there is clinical evidence of its existence, but pathological evidence of it was lacking until a recent report[18] of heart lesions in about 8 per cent of 231 necropsies in the West of Scotland neurosurgical unit. In these patients, the lesion took the form of focal myocytolysis.[19] This is seen as an area in which the muscle fibers have been removed leaving an "empty" sarcolemmic sheath, muscle nuclei lipofuscin pigment and some histiocytes. Coagulative necrosis and polymorphonuclear leukocytes are not seen (Figs 1 and 2) Less severe damage was also found in a similar number of patients.[20] The highest incidence was in patients dying of intracranial hemorrhage which may explain why the majority of reports of ECG changes in brain lesions concern patients with cerebrovascular accidents. All age groups were represented in the series and the youngest patient was a child of 4 years.

There are at least two factors which may explain why this heart degeneration has not been found previously There is a very high incidence of ischemic heart disease in the West of Scotland and some dietary factor may predispose the population to the development of cardiopathy [21,22]

Another explanation is the fairly extensive sampling of hearts which were of nor-

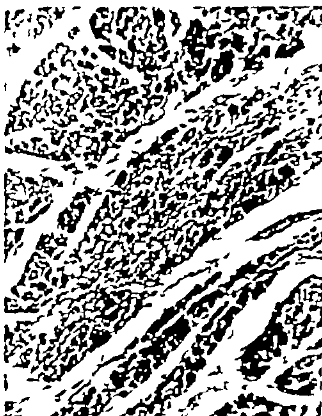


Fig 1 A focus of myocytolysis in the heart of man who died following a subarachnoid hemorrhage. Normal muscle is seen abov and below the lesion. (Hematoxylin and eosin × 150)

mal appearance. From the 18 positive cases, 170 blocks were examined and some of the 101 blocks in which lesions were found contained only one or two small foci of damage. If only one or two sections had been taken from each heart, the damage would probably have been overlooked. As with ischemic heart disease, the histological damage takes time to become apparent. Focal myocytolysis was usually found in patients who had survived for about four to six days after the onset of the neurological illness.

There are several ways in which this heart damage may be caused. Vagal stimulation in dogs causes many of the visceral lesions seen in patients dying in a neurosurgical unit. The dogs also have abnormal hearts.[23] Bradycardia and peptic ulceration are good evidence of the overactivity of the vagus in neurosurgical patients and this increase in vagal tone may cause the heart damage. There is also evidence in animal experiments which points to sympathetic overaction as the cause of cardiac dysfunction which occurs as a result of stimulation of the central nervous system (CNS). It is possible that primary overaction of the parasympathetic system may be followed by an increase in sympathetic tone in an attempt to achieve homeostasis and a combination of vagal and sympathetic overactivity has been suggested as the cause of the cardiac effects of brain stimulation.[23] Another factor which may well play a part is the release of catecholamines.[1, 26]

A study of neurosurgical patients is being undertaken in an attempt to elucidate which of these mechanisms is responsible for the effects of CNS disease on the function and integrity of the heart. It is hoped to find methods of preventing these deleterious effects. Meanwhile, it is suggested that until the role of catecholamines is better understood they should be used cau-



Fig. 2. A high-power view of the center of the lesion shown in Fig. 1. Empty sarcolemmic sheaths can be clearly seen. The nuclei are muscle nuclei and histiocytes. Polymorphonuclear leukocytes are not seen. Some remnants of muscle fiber are scattered throughout the lesion. (Hematoxylin and eosin. × 400.)

tiously in neurosurgical patients who are hypotensive as they may cause more myocardial damage.[26] More attention should be paid to abnormalities in the ECG's of these patients. Pulmonary edema can usefully be treated as being of cardiac origin.[27] Estimation of serum enzymes may help in the assessment of the extent of any myocardial changes.

Further study of these relationships between brain lesions and heart damage may throw light on the part played by stress and the hypothalamus in the causation of ischemic heart disease which is still often regarded as having a purely vascular etiology.

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Clinical communications

Prolapse of the posterior leaflet of the mitral valve occurring in eleven members of a family

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The auscultatory finding of a late systolic murmur in the mitral area often associated with a nonejection click has been noted in association with mitral incompetence.[1,2] Angiography has confirmed the presence of mitral incompetence and in a number it has been possible to show that the incompetence is associated with prolapse of the posterior cusp of the mitral valve. The subject has recently been reviewed. The pathogenesis of prolapse of the posterior cusp is unknown but the occurrence of more than one involved member in some families[2-4] suggests a genetic basis in some cases. We here report a family in whom eleven members have been found to have clinical signs compatible with prolapse of the posterior mitral valve cusp.

Clinical features

The propositus (Patient II) presented with palpitations, shortness of breath, and chest pain. A late systolic murmur in the mitral area and a nonejection systolic click were heard. These symptoms and signs were similar to those described by Barlow. In view of the known familial occurrence of this condition, the patient's relatives were contacted and examined. The family pedigree is shown in Fig. 1 and the clinical details in Table I. The abnormal cardiac signs occurred in 4 males and 7 females, the youngest being 10 years old. Apart from the propositus, only 3 subjects had symptoms. Patient II_4 suffered from mild tiredness, Patient II from angina pectoris, and Patient II from recurrent chest infections. Six subjects had both a late systolic murmur and a nonejection click, 4 had the murmur alone, and one had a click alone. These findings were confirmed in the 7 subjects who had phonocardiography. Patient II had died aged 60; a cardiologist had noted the late systolic murmur four years prior to this. All subjects were in sinus rhythm. None had added heart sounds or murmurs of mitral stenosis or aortic valve disease. No subject had a past history of rheumatic fever. Mild mitral incompetence and associated prolapse of the posterior mitral valve cusp were confirmed in the propositus by angiography.

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Table I Summary of clinical data

Patient No	Age	Sex	History of murmurs	Symptoms	Clinical
I	51	M	No	—	—
I_1	76	F	Said to have had a murmur	—	—
I	68	M	No	12 months cardiac failure vague chest pain	No murmurs
II	42	M	N	—	—
II	60	M	No	Angina pectoris	Late systolic murmur
II	59	F	N	No symptoms	No abnormalities
II	57	M	Murm r known for 39 years	Mild tiredness	Late systolic murmur
II	53	M	Purulent pericard'tis, aged 27 no murmur heard, age 37 soft systolic murmur noted, age 49	Recurrent left lower lobe pneumonia due to underlying bronchiectasis	Late systolic murmur
II	52	F	Murmur known for many year	7 years palpitations 3 months shortness of breath chest pain	Midsystolic click and late systolic murmur
III	38	M	No	Bronchial asthma	No abnormalities
III	29	F	No	No symptoms	No abnormalities
III	33	F	No	No symptoms	Midsystolic click and systolic murmur
III	38	M	No	No symptoms	Midsystolic click and systolic murmur
III	32	F	Murmur known since age 21	No symptoms	Late systolic murmur
III	28	F	No	Mild shortness of breath	No abnormalities
III	32	F	No	No symptoms	Midsystolic click
III	28	F	Murmur known since age 12	No symptoms	Midsystolic click and systolic murmur
III	14	F	No	N symptoms	No bnormalities
III	11	M	No	N symptoms	No abnormalities
III	29	F	N	No symptoms	No abnormalities
IV	13	M	N	Bronchial asthma	No abnormalities
IV	7	M	No	No symptoms	Late systolic murmur
IV	1	M	No	Bronchial asthma	No abnormalities
IV	7	F	No	N symptoms	No abnormalities
IV	10	M	N	No symptoms	N abnormalities
IV	12	F	No	No symptoms	Systolic click and late systolic murmur
IV	10	F	N	No symptoms	Midsystolic click and systolic murmur
IV	8	M	N	N symptoms	No abnormalities
IV	7	F	N	No symptoms	No abnormalities
IV	4	F	N	N symptoms	No abnormalities
IV	9	M	N	N ymptoms	N abnormalities
IV m	7	F	N	N symptoms	N abnormalities
IV	6	F	No	No symptoms	No abnormalities
IV	4	M	No	No symptoms	N abnormalities
IV	11	F	N	No symptoms	N abnormalities
IV	6	F	N	No symptoms	No abnormalities
IV m	5	F	N	No symptoms	N abnormalities
IV	7	F	N	No symptoms	N abnormalities
IV	2	F	N	No symptoms	No abnormalities

Chest x-ray	*ECG*	*Phonocardiogram*	*Progress*
—	—	—	Died suddenly age 51
—	—	—	Died age 76 of "tired heart
—	Old anteroseptal infarction	—	—
—	—	—	Died suddenly following a cerebrovascular accident
—	T-wave inversion in Leads I aV$_L$, V$_{4-6}$	—	Died, age 60, following a myocardial infarction
mal	Normal	—	—
t size at pper limit of rmal	Left ventricular hypertrophy tall T waves over mid-precordial leads	Late systolic murmur	—
rt size upper mit of normal ft lower lung acity	Normal	Late systolic murmur	—
mal	Ventricular extrasystoles S-T depression consistent with digitalis	Click and late systolic murmur	Cardiac catheter showed normal pressures left ventricular angiography showed ballooning of the mitral val cusps and mild mitral incompetence chest pains and palpitations were controlled with propranolol
—	—	—	—
mal	Normal	—	—
—	Normal	Midsystolic click	—
—	—	—	—
mal	Normal	Late systolic murmur	—
—	—	—	—
mal	Normal	Midsystolic click	—
mal	Normal	Midsystolic click and late systolic murmur	—
—	—	—	—
—	—	—	—
mal	Normal	—	—
—	—	—	—
—	—	—	—
—	—	—	—
mal	Normal	—	—
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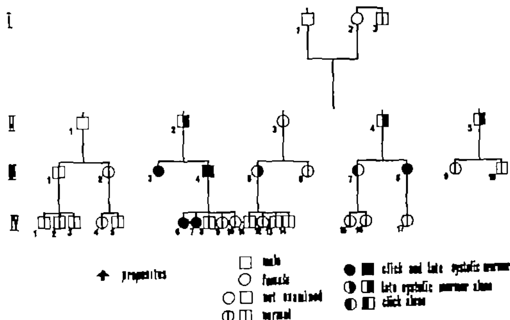


Fig. 1. Family pedigree.

Discussion

Late systolic murmurs have been described in association with Marfan's syndrome,[9] pericarditis,[10] and coarctation of the aorta[11] as well as prolapse of the posterior mitral valve leaflet. No member of our family had the stigmata of Marfan's syndrome or clinical evidence of coarctation of the aorta. The combination of a late systolic murmur with a nonejection systolic click is very suggestive of mitral cusp prolapse[3]; these signs were found in six members. A nonejection systolic click or clicks without a late systolic murmur, as in Patient II_2, may also occur in mitral cusp prolapse.[3] In view of Patient II's history of angina pectoris and associated T wave changes on the electrocardiogram, it is possible that this murmur was due to papillary muscle dysfunction; however, murmurs due to this abnormality usually show mid, rather than late, systolic accentuation.[12] Patient II_4 had purulent pericarditis at the age of 27, but no murmur was heard following this or at the age of 37. However, he has been noted to have a soft systolic murmur at the age of 49 years and this murmur has become louder recently. Some workers[13] have noted a high incidence of pericardial disease in patients with late systolic murmurs and suggest that fibrosis may distort the valve mechanism or alter the contraction characteristics of the papillary muscle[12]; this is unlikely to have caused the murmur in Patient II_4 because of the long time delay between the pericarditis and the development of the murmur.

Genetic features. An autosomal dominant form of Mendelian inheritance in our family is suggested by the involvement of approximately half the children of affected parents and involvement of both sexes. Expression of the defect appears to be delayed since, amongst the progeny of affected parents, none of the nine children less than 10 years old were involved, while six of the ten children over ten years of age were affected. Variable expressivity, which may occur in autosomal dominant conditions,[8] may result in skipped generations, and this may explain the noninvolvement of Patient II_3. It may also explain the variable clinical signs of a click alone, a murmur alone, or a click and murmur combined. Autosomal dominant inheritance of heart disease is uncommon,[1, 14] but recent reviews have discussed its occurrence in familial cardiomyopathy,[14] in some families with atrial septal defect,[14] and in some families with idiopathic hypertrophic subaortic stenosis.[14]

Pathogenesis. The primary defect leading

to prolapse of the posterior cusp of the mitral valve is not known partly because of the lack of pathologic data. Two autopsy specimens have been described. In one[3] a voluminous mitral valve cusp with thin elongated chordae was found and in the second[11] a localized expansion of the lateral portion of the posterior cusp was found. We have reported on two patients[3] with documented late systolic murmurs who developed symptomatic mitral incompetence and at operation were found to have very large posterior mitral cusps and ruptured chordae tendineae. The primary abnormality may be either a cusp that is initially larger than normal or a weakness of the posterior cusp structure predisposing to stretching. A weakness could lead to progressive enlargement and ballooning of an initially normal leaflet, and one would then expect subjects with lone clicks to later develop the murmur of mitral incompetence, but in a review of the case histories of 50 patients with posterior mitral cusp prolapse,[3] the average age of those with clicks alone was 43 years and of those with both click and murmur was 38 years. We consider the most likely defect to be a congenital enlargement of part or all of the posterior cusp resulting in mild mitral regurgitation with abnormal tension on normal chordae. The nonejection click or clicks are thought to originate from the chordae due to increased tension associated with the ballooning of the posterior cusp. This increased tension predisposes to chord rupture with the possibility of acute mitral incompetence.

Summary

A family in whom eleven members have clinical features of prolapse of the posterior leaflet of the mitral valve is described. Study of the pedigree suggests a Mendelian autosomal dominant form of inheritance in this family. The primary abnormality in this condition is unknown but primary enlargement of the cusp appears most likely and this may predispose to secondary development of mitral incompetence.

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Complex synchronized pacemaker (Atricor) malfunction

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Patients with pacemakers may develop complex arrhythmias and one must be familiar with the characteristics of a given pacemaker before attempting to interpret the findings.

The data reported herein were collected during the evaluation of a pacemaker malfunction in a 69 year-old Caucasian man who had had a synchronized pacemaker† implanted on Dec. 31 1966 for bilateral bundle branch block with intermittent complete A V dissociation and associated symptoms of a low cardiac output

The characteristics of a normally functioning Atricor are as follows. The leads are implanted directly on the surface of the heart, there being one functioning atrial sensing electrode and one functioning ventricular-stimulating electrode. If a P wave impulse of 0 9 mv amplitude or greater is conducted to the subcutaneously placed pacemaker it will trigger the pacemaker which after a delay of 0 16 sec. will stimulate the left ventricle through the ventricular electrode (Fig 1) One side of the pacemaker is metallic and serves to complete the circuit, thus, functioning as a unipolar pacemaker The maximum rate for atrioventricular synchronized beats is approximately 120 per minute above which a partial A V block occurs. A standby oscillator with a fixed rate of 58 to 62 per minute provides ventricular escape stimulation whenever electrical failure of the atria (atrial fibrillation bradycardia, or standstill) or malfunction of the atrial-sensing electrode occurs. The normal stimulus duration is 1.8 to 2 0 msec.

Approximately 15 months after implantation during a routine check in the pacemaker clinic, the patient's pulse was found to be irregular and the electrocardiogram demonstrated a variable (4 3 3.2 2 1) second degree block between the P wave and the pacemaker spike, presenting as a typical Wenckebach structure (Figs. 2A and 2B) The pacemaker spike width was normal (1 9 msec.) (Fig 3)

One week later while the atrial rate was 88 beats per minute there was an incomplete atrial-pacemaker spike dissociation with a pacemaker escape rate of 82 per minute which is abnormally rapid (Fig 4). In addition it will be noted that when carotid sinus massage slowed the atrial rate to 75 beats per minute synchronized pacing resumed temporarily A chest x-ray demonstrated the pacemaker leads to be intact (Fig 5)

An attempt to overdrive the pacemaker

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Fig. 1. Lead I of patient electrocardiogram taken on July 25, 1967 demonstrating a normally functioning synchronized pacemaker with a rate of 83 beats per minute and a P-spike interval of 0.16 sec.

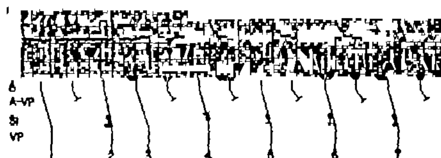


Fig. 2A. Lead VI taken on March 6, 1968. The atrial rate is 110 per minute. The pacemaker predominant response is 2:1 except in beats 2 and 3 where typical 3:2 Wenckebach period is seen. The fourth beat could be an escape from the standby oscillator (rate 58 per minute). *A*, Atrial depolarization. *A-VP*, P-spike conduction time; *SI*, standby oscillator discharge. *VP*, pacemaker-ventricular response.



Fig. 2B. Lead I taken on the same day as Lead VI in Fig. 2A. With an unchanged atrial rate, now there is constant group beating. The first beats following the pauses are probably pacemaker escapes (rate 58 per minute). Thereafter the P-spike intervals lengthen, the interspike intervals shorten, and the pauses (although terminated slightly prematurely by the escapes) are shorter than the sum of two of the shortest interspike intervals: this is the typical Wenckebach structure. See legend to Fig. 2A for abbreviations.

with a strong externally applied pacemaker stimulus to simulate the P wave demonstrated the ability of the pacemaker to synchronize its spike to the externally applied spike at a rate of 85 but not at 93 (it should synchronize up to a rate of 120) (Figs. 6A and 6B).

The decision was made to replace the pacemaker. On the day prior to surgery synchronized pacing was present with an atrial rate of 100 beats per minute, and a P-spike interval of 0.20 sec. The pacemaker was exposed under local anesthesia and when disconnected the patient was in sinus rhythm with a first degree heart block. The P wave amplitude measured from the exposed atrial lead was 1.8 mv, an adequate stimulus for a normally functioning

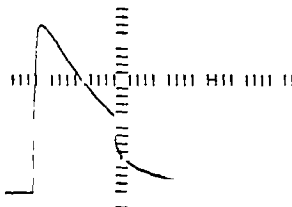


Fig 3 The pacemaker spike duration (March 3 1968) measured from the skin surface leads (Lead III) is 1.9 msec., which is within normal limits. Each vertical line represents 1 msec., and each horizontal line measures 5 m

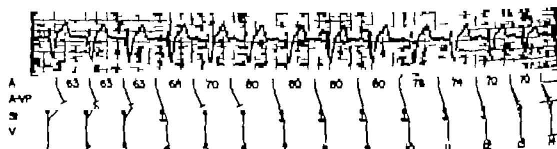


Fig 4 Lead I taken on March 14 1968 Beats 1 2 3 5 and 6 are caused by the escape of the standby oscillator which is now abnormally accelerated (rate 82 per minute). Beat 4 is slightly delayed, probably because the preceding P wave has captured the pacemaker allowing the intrinsic P-spike delay to occur Carotid sinus massage (black line) produces temporary slowing of the atrial rate (from 94 to 75 beats per minute) and beats 7 through 11 are caused by synchronized pacing (P-spike interval, 0.16 sec.). The atrial rate then increased, and beat 12 although still synchronized, is conducted with a prolonged P-spike interval (0.20 sec.). Beats 13 and 14 are fusion beats between the patient's own conducted beat (P-R interval, 0.24 and 0.26 sec.) and the pacemaker oscillator escape. The patient's own conduction is symbolized by a dotted line. See legend to Fig 2 for abbreviations



Fig 5 Chest x-ray taken on April 11 1968 shows the atrial lead (upper arrow) and the ventricular lead (lower arrow) to be in proper position without evidence of wire fracture

Atricor pacemaker The pacemaker was replaced with a demand unit which has functioned well with the patient intermittently conducting with a first degree A V block.

The pacemaker was returned to the manufacturer where a careful analysis was performed One of the batteries was found to be depleted

Discussion

When considering the malfunction of a synchronized (Atricor) pacemaker one must evaluate its several components, namely (1) atrial-sensing electrode and ventricular-stimulating electrode junctions (2) integrity of all leads (3) synchroniz



Fig 6A Lead I taken on March 21 1968 Two types of spikes can be observed, the larger one caused by an external pacemaker stimulation (*Ext.*) the smaller one (*IP*) being the patient implanted pacemaker The external pacemaker at rate of 85 per minute, captures the interval pacemaker with a spike-spike interval of 0 24 to 0.28 sec. The patient has regained A V conduction with left bundle branch block and P-R interval of approximately 0.20 sec The beat before the last is fusion the last beat is pacemaker induced. *Ext.* External pacemaker spike *IP* implanted pacemaker output V ventricular complex The patient own conduction is indicated by dotted line. See legend to Fig 2.1 for other abbreviations.

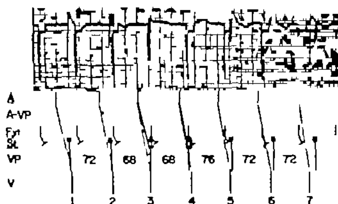


Fig 6B Lead I taken on the same day as that in Fig 6.1 The external pacemaker rate has been increased to 93 beats per minute and is now unable to capture the implanted pacemaker Spikes 1 2, 5 6, and 7 from the implanted pacer are escapes originating in the accelerated standby oscillator (rate 82 per minute). Spike 5 is slightly delayed. Spikes 3 and 4 are probably captures from the atria. Most ventricular complexes are the patient own conducted beats or fusion beats. Some ventricular complexes are very distorted by the large current generated by the external pacer See legend to Fig 2 1 for other abbreviations.

mechanism of the pacemaker (4) pacemaker output.

In our case, the pacemaker electrodes were in normal position there was no evidence of wire fracture, and the ventricles responded normally to the pacemaker spike The abnormalities present were mainly related to atrial pacemaker spike synchronization due to a block at the atrial sensing electrode junction preventing an adequate signal to reach the pacemaker and/or due to an electronic malfunction of the synchronizing device. In addition the standby (fixed) rate of this pacemaker was abnormally rapid (83 beats per minute)

Atrial pacemaker block, both incomplete and complete has been described. [4] When incomplete block was present, it was either of the first degree type (prolonged P-spike interval) or second degree type with blocked beats and a fixed P-spike interval of the conducted beats. No example of a synchro-

nized pacemaker malfunction demonstrating the Wenckebach phenomenon could be found in the literature. Fibrosis and/or necrosis of the atrial tissue around the sensing electrode was demonstrated at autopsy by Adelman and Lopez in two patients who had atrial pacemaker block.

In our case it was observed that the inability to synchronize was to a large extent rate-related as shown by the transient synchronization obtained with carotid massage. The failure of a strong externally applied stimulus to capture the internal synchronized pacemaker at a rate above 90 was evidence in favor of a malfunction of the synchronizing device of the pacemaker which under normal conditions, should follow up to a rate of approximately 120. Further evidence pointing towards pacemaker unit malfunction was obtained when an adequate signal from the exposed atrial electrode was demonstrated and in addition the abnormally rapid standby rate of the pacemaker indicated another intrinsic abnormality. Since the degree of block varied considerably during the time of observation an element of instability of the atrial sensing electrode junction cannot be absolutely excluded.

One of the most intriguing aspects of this case was the observation of the Wenckebach structure occurring between the atrial P wave and the pacemaker response. This Wenckebach phenomenon commonly observed at the A V junctional level and less frequently at the sinoatrial level results from a fundamental biologic characteristic of cardiac conducting tissue of varying its conduction velocity relative to that of the preceding beats when partial block to forward propagation of impulses is present.

Our initial impression was that the Wenckebach phenomenon observed was being produced in the atrial tissue at the atrial-sensing electrode junction. The evidence presented above however clearly demonstrated intrinsic malfunction of the pacemaker and an adequate atrial signal. Therefore the question should be raised as to whether a disturbance in the electronics of the synchronized pacemaker could cause a rhythm mimicking the Wenckebach structure so closely. Imitation of an electrophysiologic phenomenon by an artificial pacemaker has been observed, i.e. warming up of a demand pacemaker following suppression by a second fixed-rate artificial pacemaker.[4]

Summary

A complex arrhythmia in a patient with an implanted synchronized pacemaker (Atricor) is presented. It is primarily manifested by a rapid pacemaker escape rate and by first and second degree atrial-pacemaker block, the latter frequently demonstrating the Wenckebach phenomenon. Evidence is presented suggesting that this was caused by malfunction of the electronic components of the pacemaker.

The authors are indebted to Mr Walter Keller Staff Physicist of The Cordis Corporation for his careful analysis of the malfunctioning pacemaker and to Dr Richard Langendorf for his helpful criticism.

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Survival following first diagnosis of coronary heart disease

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The medical experience of the United States Army in World War II provides an exceptional opportunity to study the natural history of coronary heart disease as it appears *de novo* in a large sample of overtly healthy young men. During World War II approximately 11 million men broadly representative of the healthy adult male population of the United States served in the Army In the period of 1942 through 1945 there were about 8 000 admissions to Army hospitals for coronary heart disease. The studies of Yater and his associates [1,2] on coronary artery disease seen at necropsy in this group have already provided valuable information on certain aspects of this experience. The present study was undertaken to determine the long term prognosis of various clinical forms of coronary heart disease in relatively young males.

Materials

From July 1943 through December 1944 there were 2,234 new admissions for coronary heart disease among male Army personnel. The Medical Statistics Agency Office of the Surgeon General generously provided copies of the punched cards constituting the index to this medical experience for research purposes. The relevant diagnostic rubrics of that Agency were myocardial infarction coronary thrombosis, coronary arteriosclerosis and anginal syndrome. The file for these diagnoses included 05 men who either died

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within 24 hours following admission were dead on arrival or were found dead. The original Army medical records for the 2,234 men were systematically abstracted for information on past history, present illness, findings at admission and during hospitalization, course in the hospital, and condition at discharge. The records of subsequent admissions to Army and Veterans Administration hospitals, of examinations for disability evaluation, and of deaths, were similarly abstracted in a standard format. In the abstract, the original Army diagnosis, which often was expressed in somewhat different language from that of the code rubric, was recorded.

Recent methodologic studies of the Follow-up Agency indicate that the ascertainment of the mortality rate among World War II veterans, based on records of the Veterans Administration, is 98 per cent complete. Only in rare instances does the death of any veteran fail to become a matter of record in the Veterans Administration. Inasmuch as about one third of the observed deaths occurred during Army service, and these are completely reported, the maximum error of death ascertainment for this 15 year follow-up is probably less than 2 per cent.

Procedures and criteria for review diagnosis

Since the Army diagnoses represented the judgments of a large number of clinicians of varied training and background, it seemed important to review each case in the light of current diagnostic criteria in order to provide a more uniform up-to-date classification of the material. Each of the reviewers (W. J. Z. and T. W. M.) was provided with photocopies of the clinical summary of the original Army hospitalization, of all electrocardiograms (ECG's) and laboratory findings, but with the hospital diagnoses and ECG interpretations excluded.

There were 205 patients who were dead on arrival or died within 24 hours after admission. We attempted to establish their diagnosis by reviewing any available autopsy reports, any medical histories from previous admissions for other diagnoses, and similar relevant information. For 77 men in this group the available autopsy information was sufficiently specific to permit their inclusion in the diagnostic classifications employed in the study. There were in addition 128 sudden deaths for which available information was too scant or not sufficiently specific to assign a review diagnosis. Autopsy reports supporting the diagnosis of coronary occlusion or thrombosis were accepted for 72 cases and in 50 others no information was found which might rule out these diagnoses. It seems clear that exclusion of these 122 unconfirmed early deaths would surely lead to underestimation of the initial mortality rate for coronary heart disease and to neglect of an important aspect of prognosis.[3] Since these men were believed by Army physicians to have died of coronary heart disease, they have been retained in the series for supplementary analysis.

The review diagnoses were formulated for each case without consultation between the reviewers. These diagnoses were grouped in the following categories.

Myocardial infarction. Included in this category were cases that showed evolving ECG changes considered diagnostic of myocardial infarction and supported by a compatible history related to the acute event, and cases without the ECG showing recent myocardial necrosis on autopsy.

Coronary occlusion. Findings grouped here include clinical symptoms and signs compatible with acute myocardial infarction, but death occurring before the ECG was recorded. On autopsy the cases in this group showed a severely narrowed segment of a coronary artery, but without thrombus and without evidence or mention of myocardial necrosis.

Coronary thrombosis. Cases grouped here showed an autopsy finding of a fresh thrombus in a coronary artery, but without evidence or mention of myocardial necrosis. The history was compatible with recent myocardial infarction.

Coronary insufficiency. Findings grouped here include clinical symptoms and signs compatible with myocardial infarction but of duration less than one-half hour and minor S-T or T changes on the ECG not diagnostic of myocardial infarction. Subendocardial infarctions could not be excluded from this category because absence

of enzyme determinations and limited ECG's made such diagnostic precision impossible.

Angina pectoris Included in this category were cases that showed characteristic symptoms with effort or excitement, relieved by cessation of the precipitating activity The ECG was normal or showed minor or nonspecific S-T or T wave changes.

Coronary arteriosclerosis Cases grouped here showed an autopsy finding of arteriosclerosis or atherosclerosis of the coronary arteries without evidence or mention of thrombosis or myocardial necrosis. The circumstances of death were not observed or inadequately described

Heart block For this group the symptoms included intraventricular block found on the ECG and a QRS duration of 0.12 sec. or greater A V block was not considered evidence of coronary disease in the absence of other diagnostic ECG changes or clinical findings.

Other or unspecified coronary heart disease Grouping in this category was based on electrocardiographic evidence of old myocardial ischemia found on admission for another cause, the duration uncertain

Other heart disease For this group the electrocardiographic abnormalities were more consistent with pericarditis, myocarditis, ventricular hypertrophy atrial fibrillation or other arrhythmias, but not characteristic of coronary disease The clinical history was not suggestive of coronary disease.

Not heart disease Cases in this category had neither clinical history nor ECG support diagnosis of coronary heart disease.

Unknown For this category there were inadequate or illegible records, no diagnosis, etc.

In the review of the recorded medical histories the following symptoms were accepted as consistent with acute myocardial infarction severe crushing pressure tightness or pain of the retrosternal location with radiation to the arms, neck jaw or back. Persistence of such severe discomfort for more than 20 minutes or the necessity for opiates for relief favored this probable diagnosis. Signs of vascular collapse were further support for this diagnosis.

Retrosternal pain tightness or pressure developing on exertion and usually requiring cessation of the precipitating exertion with relief within minutes was considered consistent with angina pectoris. Radiation to the ulnar area of one or both arms to the neck, or to the jaw was additional support for angina pectoris.

The same symptoms of moderate severity persisting for up to half an hour and associated with signs of pallor cold sweat, rapid thready pulse or other signs of partial vascular collapse during this period were considered an intermediate syndrome of coronary insufficiency

A variety of less typical symptoms such as acute dyspnea nausea indigestion and palpitation were accepted where associated electrocardiographic findings supported a coronary diagnosis

Serial electrocardiograms were available for most cases surviving long enough for hospital workup however only the standard limb Leads I II and III and one precordial Lead CF or V_4 were routinely being taken at this period in 1944 Additional precordial leads were more often recorded on subjects admitted to larger hospital centers where consultation services were available. Twelve-lead ECG's were also a normal part of subsequent medical evaluations for disability or as part of subsequent medical records in Veterans Administration hospitals after discharge from the Army

Standard electrocardiographic criteria[4-] for evidence of myocardial necrosis, injury and ischemia were familiar to each reviewer however individual training and experience undoubtedly influenced the interpretations particularly in borderline abnormalities.

One reviewer T W M had considerable years of experience including responsibilities of cardiology services in teaching general hospitals of the Department of the Army and consulting and teaching responsibilities in civilian institutions since retirement from the military service The other reviewer W J Z had primary experience in the interpretation of ECG's in large epidemiologic studies of coronary heart disease In addition to measurement criteria for Q-wave amplitude and duration and identification of S-T and T changes in

serial ECGs the latter reviewer applied Grant's[7] technique of vector analysis to classify borderline ECGs.

Comparison of reviewers' diagnoses

While each reviewer was able to accept the evidence provided as adequate for a diagnosis of some form of coronary heart disease in the majority of cases so classified there was considerable difference between the reviewers as to the exact diagnostic category to which each case should be allocated (Table I)

Somewhat better agreement was seen in the classification of cases as myocardial infarction where 560 cases were independently assigned this diagnosis by both reviewers. Greater differences were seen

Table I *Diagnoses independently made by two reviewers*

Reviewer B	Reviewer A									
	Total	MI	CO CT	CI	AP	CA	HB	Other HD	Not HD	Unknown
Total	2 234	643	54	262	665	3	33	167	129	276
MI	853	560*	11	99	116	—	1	38	17	11
CO CT	89	14	38	13	11	3	—	—	6	4
CI	255	21	2	47*	140	—	1	24	11	9
AP	204	1	1	17	162	—	1	6	6	10
CA	21	—	1	2	5	—	1	6	1	5
HB	27	3	—	1	6	—	13	—	3	1
Other HD	192	20	—	34	45	1	13	50*	18	11
Not HD	161	8	1	23	67	—	2	18	27*	15
Unknown	432	16	—	26	113	1	1	25	40	210*

Abbreviations Myocardial infarction (MI) coronary occlusion or thrombosis (CO, CT); coronary insufficiency (CI); angina pectoris (AP) coronary arteriosclerosis (CA) heart block (HB) other heart disease (Other HD); not heart disease (Not HD).
*Indicates agreements in diagnosis between the two reviewers.

Table II *Distribution of Caucasian male patients by age at reference point* and by final Army hospital diagnosis*

Age at reference point (yr)	Diagnostic group							
	MI CO CT		AP CI		Other		Total	
	No.	%	No.	%	No.	%	No.	%
Less than 29	113	11 1	34	4 9	14	3 9	161	7 8
30 to 34	184	18 0	75	10 9	37	10 4	296	14 3
35 to 39	282	27 6	213	30 9	66	18 5	561	27 2
40 to 44	175	17 2	158	22 9	68	19 0	401	19 4
45 to 49	146	14 3	131	19 0	70	19 6	347	16 8
50 to 54	77	7 5	54	7 8	55	15 4	186	9 0
55 to 59	35	3 4	17	2 5	35	9 8	87	4 2
60 and over	8	0 8	7	1 0	12	3 4	27	1 3
Total known	1 020	99 9	689	99 9	357	100 0	2 066	100 0
Age unknown	—		1		—		1	
Total	1 020		690		357		2 067	

Abbreviations MI, Myocardial infarction CO, coronary occlusion; CT coronary thrombosis AP angina pectoris; CI, coronary insufficiency
*The beginning of observation for survival or mortality the reference point is taken as the date of admission to the Army hospital in which the diagnosis of heart disease was first made. For the sudden deaths, the date of death is used.

in the classification of cases as coronary insufficiency or angina pectoris where more subjective interpretations of symptoms in the absence of characteristic ECG changes resulted in a greater overlap of such diagnoses.

In addition to the cases in which information was considered sufficient to allow a review diagnosis, there were 210 cases in which neither reviewer could arrive at a diagnosis. Within this group were 182 for whom no ECG's or other definitive information were available. The 128 undiagnosed sudden deaths were included in this group.

Findings on mortality and survival

Because of the relatively young age of the Army population from which these cases were arising, the series is younger than others reported in the literature.[6-13] Fifty two per cent of cases diagnosed as coronary disease were under 40 years of age, the youngest being 19 years of age and the oldest 70 years of age at the time of the first attack. The age distribution of the 2 067 Caucasian males in this series is shown in Table II. Survival experience is presented according to the classification of original Army hospital final diagnoses. For these analyses the more severe syndromes of myocardial infarction, coronary occlusion, and coronary thrombosis have been combined. Likewise, the two milder clinical syndromes of angina pectoris and coronary insufficiency have been combined.

Survival experience for the entire series of coronary cases as originally classified by Army hospital diagnosis is shown in Table III. For white males diagnosed to have myocardial infarction, coronary occlusion, or coronary thrombosis 15 per cent died before they could be admitted or within 24 hours after admission for their attack. For angina pectoris or coronary insufficiency, less than 1 per cent died within the first day, and for those men diagnosed to have nonspecific arteriosclerotic heart disease 8 per cent died within the first day. Survival percentages at intervals to 15 years are shown in Table III according to the original medical diagnosis. The experience is least favorable

Table III *Percentage of survivors at selected intervals after reference point* by Army hospital diagnosis and by race*

Race and interval after reference point	*Total*	*Army hospital diagnosis:* *Myocardial infarction, coronary occlusion, coronary thrombosis*	*Angina pectoris coronary insufficiency*	*Nonspecific arteriosclerotic heart disease*
		Percentage surviving		
Caucasian				
Up to one day	91 0	85 1	99 3	91 9
1 wk.	90 1	83 3	99 1	91 3
1 mo.	89 7	83 0	99 0	91 0
1 yr	86 5	78 3	97 7	88 2
5 yr	77 4	67 5	90 1	80 7
10 yr	65 4	54 4	79 7	69 2
15 y	55 0	41 9	71 1	57 2
		No. of men		
No. alive at reference point	2 067	1 020	690	357
Nonwhite or unknown race (No. of men)	167	70	59	38
Total sample	2 234	1 090	749	395

*The beginning of observation for survival or mortality "reference point," is taken as the date of admission to the Army hospital in which the diagnosis of heart disease was first made. For cases of sudden death, the date of death is used.

for the men diagnosed to have myocardial infarction coronary occlusion or coronary thrombosis, and most favorable for the men originally diagnosed to have angina pectoris or coronary insufficiency At the end of ten years, only 54 per cent of the first group survived in contrast to 80 per cent in the angina–coronary insufficiency group and 69 per cent in the nonspecific arteriosclerotic heart disease group These differences reflect more than the initial case fatality Of men who were alive at the end of one year death subsequently claimed 47 per cent of the group with infarction 27 per cent of those with angina pectoris and 35 per cent of those with nonspecific arteriosclerotic heart disease by the end of the fifteenth year This survival experience of men classified by the original Army medical diagnosis is more favorable than found for the men in comparable diagnostic categories classified by criteria of the reviewers.

In the absence of an external criterion of validity for the review diagnoses it seemed best to define confirmed cases as those agreed upon by both reviewers, working independently of each other and of the original Army diagnoses. As may be seen from Table I there were 623 (560+ 11 + 14 + 38) in the infarction–occlusion–thrombosis categories, and 366 (47 + 140 + 17 + 162) in the insufficiency–angina categories. For Caucasian men only the corresponding figures are 598 and 351 Unclassifiable sudden deaths are excluded from the above counts. At diagnosis the infarction–occlusion–thrombosis group was somewhat younger than the angina–coronary insufficiency group (Table IV and cf also Table II) In the confirmed infarction–occlusion–thrombosis group, 9 per

Table IV Number and per cent of Caucasian male patients with confirmed coronary heart disease by age at reference point and by review diagnosis

Age at reference point	Review diagnosis: MI CO CT N	MI CO CT %	AP CI No.	AP CI %
20 to 29	45	7 5	15	4 3
30 to 34	106	17 7	42	11 9
35 to 39	160	26 8	96	27 3
40 to 44	107	17 9	92	26 1
45 to 49	95	15 9	63	17 9
50 to 64	85	14 2	44	12 5
Total	598	100 0	352	100 0

Abbreviations: MI Myocardial infarction; CO, coronary occlusion; CT coronary thrombosis AP angina pectoris; CI, coronary insufficiency

Excluding one of unknown age at onset.

Table V Percentage of survivors at successive intervals after the reference point Caucasian males only by review diagnosis

Interval after reference point	Confirmed MI CO CT*	Confirmed AP CI	Not confirmed† or possible heart disease
Up to one day	91 0	99 4	97 2
1 day	90 1	99 4	96 8
2 days	90 0	99 4	96 7
3 days	89 6	99 4	96 7
4 days	89 6	99 4	96 5
5 days	89 3	99 4	96 5
6 days	89 3	99 4	96 3
2 weeks	89 0	99 4	96 2
3 weeks	88 6	99 4	96 2
4 weeks	88 6	99 4	96 2
1 yr	83 3	97 7	93 4
2 yr	79 1	96 0	91 3
3 yr	75 8	92 4	89 8
4 yr	72 9	90 7	88 1
5 yr	69 6	89 5	85 3
6 yr	66 1	86 7	84 3
7 yr	62 4	82 4	82 6
8 yr	58 7	81 0	80 6
9 yr	54 5	79 0	78 8
10 yr	50 9	75 4	76 4
11 yr	48 5	72 0	73 3
12 yr	45 2	70 5	71 2
13 yr	43 0	68 3	68 9
14 yr	38 8	65 0	67 2
15 yr	37 7	63 5	66 6
No. of men	598	353	851

Abbreviations MI, Myocardial infarction; CO, coronary occlusion CT coronary thrombosis AP angina pectoris CI, coronary insufficiency

*Sudden deaths are not included unless the two reviewers agreed on the diagnostic classification by applying the criteria of the review

†A case is not included if both reviewers agreed that it is not heart disease or that it cannot be classified.

cent died immediately (Table V) Not included in this figure are 117 sudden deaths in the total series of 2 067 Caucasian males for whom no review diagnosis could be made but most of whom probably fall into this group as judged by autopsy findings or the circumstances of their death In 91 of these 117 cases a subsequent detailed review failed to uncover evidence of any other disease which could explain the deaths. After ten years, survival is 51 per cent in the confirmed infarction–occlusion–thrombosis group in contrast to 75 per cent in those with angina or coronary insufficiency and 76 per cent in the residual group By 15 years these values were reduced to 38 64 and 67 per cent.

If the 117 early deaths are added to the 598 confirmed cases of infarction occlusion, or thrombosis, the immediate case fatality rate rises from 9 to 24 per cent and survival after 15 years is lowered from 38 to 32 per cent. The survival percentages based on the review diagnosis are somewhat lower than those based on the original Army medical diagnosis especially when the 117 early coronary deaths for which no review diagnosis could be made are included with the confirmed infarction–occlusion–thrombosis group For example, after 15 years the comparative survival percentages are as follows by diagnostic group (Table VI)

In the confirmed infarction–occlusion–thrombosis group (diagnostic group MI–CO–CT in Table VII) age at initial diagnosis has an important bearing on early fatality Summarized below are case fatality rates for the first year by age group with the 117 sudden deaths excluded from consideration (top) or included (bottom) In the age group 20 to 29 the early case fatality rate is slightly higher than in the other age groups when the unconfirmed sudden deaths are not considered When the immediate fatalities are included the rate in the youngest age group is considerably higher than in the other groups. No appreciable differences with age were found in the early mortality rate of the diagnostic group of angina pectoris–coronary insufficiency

The survival experience in the 15 years following hospitalization is given by age and diagnostic group in Table VIII In both diagnostic groups the proportion of survivors among the youngest men is somewhat greater at the end of the follow up period than among men in the older age groups. This finding contrasts with the higher early mortality rate of the young patients and suggests that death associated with aging affects the older age groups. A

Table VI *Comparison of survival percentages*

Diagnostic group	*By Army diagnosis*	*By reviewers confirmed diagnosis*	*By reviewers confirmed diagnosis plus early deaths*
Infarction–occlusion–thrombosis	42	38	32
Angina–insufficiency	71	64	64

Table VII *Comparison of fatality rates*

Diagnostic group MI CO CT	*Age group*			
	20–29	*30–39*	*40–49*	*50–64*
Confirmed review diagnoses excluding sudden deaths	24 4	18 0	12 9	17 6
Confirmed review diagnoses including sudden deaths	47 7	32 9	23 8	25 5

Table VIII Percentage of survivors by age year after admission and review diagnosis, Caucasian males sustaining first coronary heart disease

Myocardial infarction coronary occlusion coronary thrombosis							Angina pectoris coronary insufficiency						
Age	Yr after admission					Total N	Age	Yr after admission					Total N
	1	5	7	10	15			1	5	7	10	15	
20 to 29	75 6	71 1	71 1	60 0	45.3	45	20 t 29	100 0	100.0	86.7	80.0	80 0	15
30 to 39	82.0	66 5	63 5	50 4	40 8	266	30 to 39	97.8	90.6	84 1	77.5	71.1	[illegible]
40 to 49	87 1	71.8	62 9	52.5	39 2	202	40 to 49	96.8	87 7	81 9	74.8	63 2	153
50 to 64	82 4	64 7	52 9	43 5	27 6	85	50 to 64	100 0	88.6	77.3	68.2	36 3	44
Total	83 3	69 6	62 4	50 9	37 7	598†	Total	97 7	89 5	82.4	75 4	63.5	[illegible]

*Values for 1 year survival

†Sudden deaths are not included unless the two reviewers agreed on the diagnostic classification by applying the criteria of the text.

‡Includes one case of unknown age.

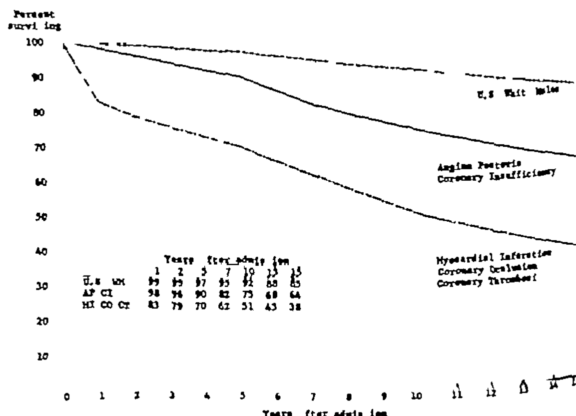


Fig 1 Per cent of survivors by year after admission and review diagnosis. Caucasian males surviving first coronary heart disease compared to United States Caucasian male cohort of same age composition.

comparison of the attrition among patients with that expected in a group of American Caucasian males of the same age composition is shown in Fig 1 In the confirmed infarction–occlusion–thrombosis group the yearly mortality rate, as indicated by the slope of the curve is highest in the first year (16 7 per cent) and subsequently remains relatively constant at about 5 per cent per year In the confirmed angina pectoris–coronary insufficiency group the yearly mortality rate is fairly constant throughout the follow-up period at about 3 per cent. The mortality rate of United States Caucasian males increases throughout this period approaching the rate of the coronary patients at the end of the 15 year period

The improvement over time in survival of patients relative to that of the United States Caucasian male population at risk in the same calendar period is shown by age in Fig 2 The mortality ratio of the observed deaths among patients in the confirmed infarction–occlusion–thrombosis group to deaths expected among United States Caucasian males of the same age is presented for different intervals in the follow-up period The bars in Fig 2 indicate the width of the 95 per cent confidence limit around the central value of the mortality ratio. The value for the first year in the age group 20 to 39 is much higher than the other values and could not be plotted without reducing the scale excessively The numeric values of the mortality ratio are shown across the top of the figure The mortality ratios decline consistently with age and duration of follow-up so that the mortality rate of patients in the oldest

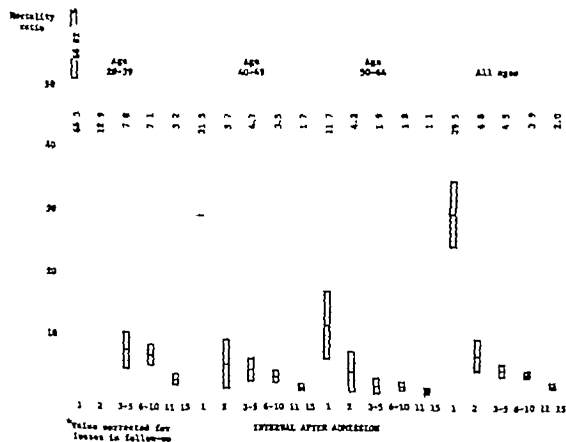


Fig 2 Mortality ratio and 95 per cent confidence limits of the mortality ratio of patients to American Caucasian males of the same median age, by age group and interval after admission. Caucasian males with confirmed diagnoses of myocardial infarction, coronary occlusion, and coronary thrombosis.

age group is essentially the same at the end of the follow-up period as among American Caucasian males. In the group of confirmed angina–insufficiency the mortality ratios in the different time intervals had considerable variability but values for the entire follow-up period did decrease with age. They were 3.46, 2.15, and 1.84, respectively, for the age groups 20 to 39, 40 to 49, and 50 to 64.

Discussion

Relatively few studies have been reported on the natural history or long term prognosis of men who have sustained a first clinical occurrence of myocardial infarction or angina pectoris below the age of 40. More information has been reported on the outcome of myocardial infarction among men above the age of 40 at the date of onset of their first clinically diagnosed attack.

The present study was undertaken to take advantage of a large roster of young coronary cases diagnosed over a relatively short interval of time (18 months) within the United States Army during a peak period of its mobilization in 1943-44 when nearly 11 million men were on active duty. The requirement for a medical examination on entry into the service provided reasonable assurance that major concomitant diseases would not be present in this group to alter the subsequent natural history of the diagnosed coronary disease.

The further assurance that the fact of death or survival could be determined without significant loss to follow-up through the Veterans Administration mechanisms was an additional asset. The limitations of these medical records are, however, recognized, particularly in the diagnostic information available on borderline cases. Even with the limited number of electrocardiographic leads used in routine diagnosis at this period, the evidence from serial changes was often more than adequate to confirm a diagnosis of myocardial infarction by both reviewers working independently. This was less certain for the borderline cases where additional unipolar limb leads and precordial leads would have been useful. Likewise, it would have been helpful if current laboratory procedures for detecting elevations of serum enzyme levels indicative of myocardial necrosis would have been available to help in the diagnosis of uncertain cases. Despite the limitations of such medical records, a fairly high probability of confirmation of diagnosis could be established on a relatively large group of young men diagnosed to have had a first clinical attack of coronary heart disease while in Army service.

The findings support other studies in confirming the high, early case fatality rate associated with myocardial infarction. The problem of determining the proportion of sudden deaths which are caused by this disease or the mechanism of such deaths remains to be answered. Only 9 per cent of confirmed myocardial infarction–coronary occlusion–coronary thrombosis cases died within the first 24 hours after hospital admission. However, a group of additional sudden deaths was assigned as due to coronary disease by Army physicians and acceptance of their judgment for this group of cases where adequate data for review were lacking would increase the early case fatality rate to 24 per cent. Even in the presence of autopsy exploration, no cause of death could often be clearly ascertained.

The unusually high, early fatality rate for men in the 20 to 29 year age group in this series diagnosed to have myocardial infarction, coronary occlusion, or coronary thrombosis is contrary to findings from other series where a more favorable outcome from myocardial infarction has been suggested for younger men.[8-11] The men in the younger decades who survived their myocardial infarction for one year showed a more favorable long term survival than did men in the older decades (Table VIII). This does not imply that it is better to have a myocardial infarction at a young age, since the excess mortality compared with the same age men in the general population is still appreciable (Fig. 2).

Another finding from this study was that the prognosis for men diagnosed as having first clinical manifestations of angina pectoris or the intermediate syndrome of coronary insufficiency was appreciably more favorable than for men whose initiating episode of coronary disease was presented as myocardial infarction, coronary occlusion, or coronary thrombosis. This favorable relationship was found

for each age group and at each interval through the 15 years (Table VIII) These data support the studies reported by Richards and associates[11] rather than the findings from a clinicopathologic study reported by Francis and associates.

The long term survival of confirmed cases of myocardial infarction is considerably better than that given in most other studies. We do not believe that this represents misdiagnosis since the evidence was sufficient for both reviewers to independently agree with the classification of subjects to this category Two factors are present in this series which differ from previously published studies and favorably influence the results. The first factor is the absence of major complicating diseases often found in selected hospital population series or even in studies from general civilian or employee populations. The second factor is the inclusion of a wider spectrum of clinical cases of disease as evidenced from the finding that 18 per cent of reviewer-confirmed cases of myocardial infarction were discovered as a result of routine medical examinations, admission for symptoms not initially considered coronary disease or admission for coronary symptoms but not presenting as a severe attack. A more detailed presentation of the relationship of clinical factors to survival from coronary heart disease in this group will be the subject of a separate report.

Summary

1 Survival tables over a 15 year period are presented for white males between the ages of 20 through 64 who were diagnosed to have a first clinical occurrence of coronary heart disease while in Army service. Diagnostic groupings for this analysis were separated into two categories myocardial infarction–coronary thrombosis-coronary occlusion and angina pectoris–coronary insufficiency

2 Both the immediate prognosis for survival and the prognosis over the 15 year period were less favorable for cases initiating as myocardial infarction–coronary thrombosis–coronary occlusion than for cases initiating as angina pectoris-coronary insufficiency

3 The first 24 hours after onset of clinical manifestations of either group of coronary disease syndromes was the period of the highest concentrated mortality rate.

4 At all ages the myocardial infarction–coronary occlusion–coronary thrombosis group had a higher mortality rate (16 7 per cent) in the first year of follow-up than in any subsequent year After the first year the annual mortality rate in this group was about 5 per cent and did not vary much with length of follow-up In the angina pectoris–coronary insufficiency group the annual mortality rate was about 3 per cent throughout the follow-up period

5 Comparison of the observed mortality rate in the infarction–thrombosis–occlusion group with that expected for American males of the same age and race in the same calendar period reveals a steady decrease in the mortality ratio (observed/expected) from about 30 in the first year to approximately 2 in the interval 11 15 years after diagnosis. In both diagnostic groups, mortality ratios of older patients were lower than those of younger patients.

The conduct of this study depended on medical and other records of the Department of Defense, the Veterans Administration, and the National Archives and Records Service, General Services Administration. We are indebted to these agencies, particularly to their records management personnel, for the ready access that they generously provided to the required material

We gratefully acknowledge the assistance of the staff of the Follow-up Agency: Mr A. Hiram Simon, Chief of Operations Miss Vivian A. Heidenblut, the supervisor directly responsible for records abstracting and coding and Mrs. Lucille P Pogue for computational and analytic work.

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Chaotic atrial mechanism

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The atrial arrhythmias have been the subject of numerous reports. However, one particular atrial arrhythmia has received little attention. This one is a disorganized type of rhythm which we have termed chaotic atrial mechanism (CAM). This arrhythmia is a distinct and important entity, and the purpose of this paper is to define it clearly and present the results of clinical and pathologic studies performed over a two year period in 31 patients in whom the disturbance has been detected.

The atrial arrhythmia under consideration here is characterized by (1) clearly recognizable P waves of at least three wave forms in one lead of the electrocardiogram, (2) the absence of one single persistent dominant atrial pacemaker (in distinction to normal sinus rhythm with multiple and multifocal atrial premature beats), (3) variable P-P intervals, R-R intervals, and P-R intervals. The atrial impulses may be conducted normally through the ventricles or they may be conducted with bundle branch block pattern or with intraventricular aberration. Generally, each P wave is conducted to the ventricles, but nonconducted impulses occur at times.

On physical examination in the presence of this arrhythmia, a diagnosis of atrial fibrillation is usually made before the electrocardiogram is obtained. Because of the gross disorderliness of the rhythm with distinct but quite variable P waves, the term chaotic atrial mechanism (CAM) seems to be appropriate. Electrocardiograms in Figs. 1 through 4 illustrate this rhythm disturbance.

Material and methods

Chaotic atrial mechanism was diagnosed in 31 patients according to criteria noted above. The following information was obtained on each patient: age, sex, race, complete history, physical findings, complete blood count, urinalysis, carbon dioxide combining power, serum electrolytes (chloride, sodium, potassium), fasting blood sugar, and blood urea nitrogen. Serum glutamic oxalacetic transaminase, lactic dehydrogenase, pulmonary function studies, blood gas determinations, radiographic findings, and bacteriologic studies of spu

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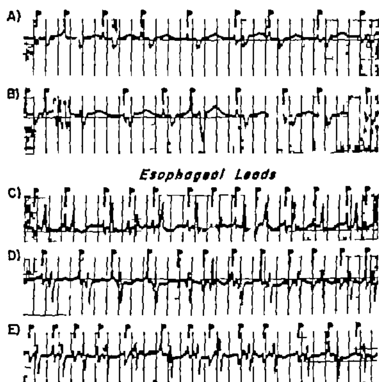


Fig. 1. A and B, Lead V. The changing contour of the "P" waves and variation in P-P, P-R, and R-R intervals are evident. C, D, and E, Esophageal leads recorded during breath holding to avoid respiratory artifact. The chaotic nature of the arrhythmia and changing form of the "P" waves are clearly evident. Some intraventricular conduction aberration is also evident.

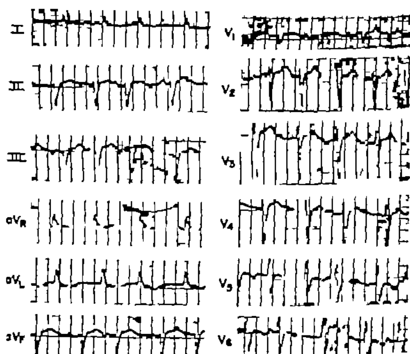


Fig. 2. Routine 12 lead electrocardiogram illustrating an example of chaotic atrial mechanism

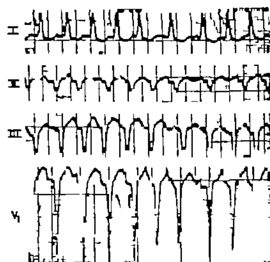


Fig. 3. Electrocardiogram demonstrating the rapid rate which occurs on occasion in chaotic atrial mechanism. Varying contours of the "P" wave are shown.

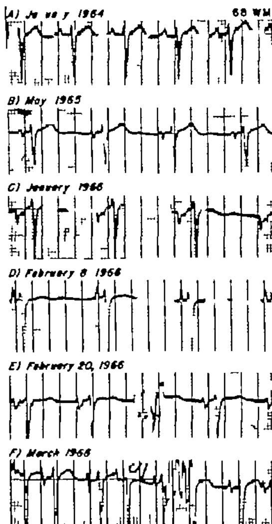


Fig. 4. Serial recordings of Lead V in a 68-year-old Caucasian male who had recurrent myocardial infarctions and who exhibited definite electrocardiographic evidence of atrial disease prior to the onset of the chaotic atrial mechanism. Although the atrial pacemaker site apparently shifted from one recording to another, it is interesting that each focus remained fairly stable until the onset of the chaotic mechanism illustrated in strip F.

tum blood and urine were recorded where indicated. All electrocardiographic abnormalities were noted and serial electrocardiograms were obtained to ascertain correlation with other arrhythmias and abnormalities. The relationship with medication, especially digitalis and other cardioactive drugs, was investigated. Glucose tolerance tests were done in 9 patients and two hour postprandial blood glucose levels in 5 others. Where glucose tolerance tests and two hour postprandial blood sugar levels were not obtained, serial fasting blood glucose determinations were done. Sixteen of 31 patients died during the study; autopsies with gross and histologic studies were performed on 8. The data were then assembled, tabulated, and analyzed.

Results

Incidence, rate, and duration of the arrhythmia. About 12,000 electrocardiograms are interpreted annually at the Veterans Administration Hospital in New Orleans. Since only 31 instances of CAM were detected in two years, it is obvious that the arrhythmia is not particularly common. No doubt it is sometimes overlooked. A sex ratio cannot be given because the population of this hospital is predominantly male. Of the 31 patients studied 25 were Caucasian and 6 were Negro. The patients were all advanced in age, the youngest being 53 years and the eldest 80 years of age. The average age was 68.5 years. This advanced age probably reflects in part the characteristics of the hospital population.

As indicated in Table I, the cardiac rate was variable, but it was usually in the tachycardia range (chaotic atrial tachycardia), being between 101 and 150 beats per minute in 61 per cent of patients. One

Table I Ventricular rate with chaotic atrial mechanism at the time of initial diagnosis

Ventricular rate (beats/minute)	N of patients	%
56 t 75	5	16 1
76 to 100	6	19 4
101 to 150	19	61 3
151 t 200	1	3 2
Total	31	100 0

Table II Maximum observed duration of chaotic atrial mechanism in each patient studied

Duration (day)	N of patients	%
< 3	6	19 4
4 10	12	38 7
11–30	7	22 6
31 365	4	12 9
> 365	2	6 4
Total	31	100 0

patient had recognizable variable P wave at a rate of 170 to 200 per minute shortly before death (Fig 3) The arrhythmia was noted to continue for as short a period as a few seconds up to months or even years (Table II) One week was usually the known duration but two patients were followed who exhibited the arrhythmia for more than a year The disorder was intermittent in some patients and persistent in others. Obviously the exact duration in each instance was not established since serial or continuous electrocardiograms could not be obtained in all patients throughout the duration of the arrhythmia.

Symptomatology Dyspnea was the predominant symptom associated with the arrhythmia. Although many of the patients were seriously ill with cardiac and/or pulmonary disease it appeared that dyspnea was distinctly more severe during the time of the arrhythmia One patient had several bouts of acute pulmonary edema following each onset of CAM Palpitation and weakness were other symptoms noted regularly.

Pulmonary disease It was apparent early after initiation of the study that obstructive lung disease and diabetes mellitus frequently coexisted in patients with the rhythm disturbance These are common disorders in the hospital population under study but their occurrence in association with CAM was disproportionately high. Significant chronic obstructive lung disease as determined by pulmonary function studies was present in 26 patients (83.9 per cent) Clinically diagnosed cor pulmonale existed in 17 patients (54.8 per cent) Pulmonary infarction was documented in one patient and strongly suspected in 4 others. Carcinoma of the lung was found in 2 patients.

Standard bicarbonate pCO_2, pO_2, and pH were obtained in 16 patients. There was no consistent pattern nor could a clear correlation be established between the arrhythmia and these laboratory data. This was true also for electrolyte determinations obtained in all patients.

Diabetes mellitus There was an unusually high incidence of diabetes mellitus in the patients under study Five patients were known diabetics on treatment. Glucose tolerance curves were interpreted using the criteria of Fajans and Conn[1] with appropriate corrections for age According to these criteria 8 of 9 additional patients tested proved to be diabetic. Two hour postprandial blood sugars were abnormally elevated in 4 of the 5 additional patients so tested and there were two or more definitely elevated fasting blood glucose determinations in each of 4 other patients Thus, diabetes mellitus was diagnosed or strongly suspected in 21 patients (68 per cent) As an outgrowth of this study initiated by the detection of the arrhythmia, more than 10 patients with previously unrecognized diabetes were discovered. It should be noted that in a few instances it was difficult to decide whether true diabetes mellitus or so-called senile diabetes [2] was present.

Electrocardiographic analysis Careful evaluation of serial electrocardiograms in these patients yielded information shown in

Table III Atrial arrhythmias observed during absence of CAM (total serial electrocardiographic review)

Arrhythmia when CAM absent	No. of patients
Premature atrial contractions (frequent)	19
Sinus tachycardia	12
Atrial fibrillation	7
Atrial flutter	5
Atrial bigeminy	2
Paroxysmal atrial tachycardia with block	2
Wandering atrial pacemaker	2
Supraventricular tachycardia	2
Sino-atrial block	1

Table IV Observed relationship of CAM with other atrial arrhythmias

Arrhythmia	No. of patients
Preceding CAM	
Atrial fibrillation	4
Atrial flutter	3
Atrial tachycardia	3
Paroxysmal atrial tachycardia with block	1
Wandering pacemaker	1
Following CAM	
Atrial flutter	3
Atrial fibrillation	2
Paroxysmal atrial tachycardia with block	1

Tables III-V Atrial arrhythmias other than the one described were not uncommon in these patients at times when CAM was not present (Table III) Premature atrial contractions were frequent in number both before onset and after termination of CAM Of particular interest was the finding of CAM preceding or following episodes of atrial flutter atrial fibrillation or paroxysmal atrial tachycardia with A V block in several patients (Table IV)

Other electrocardiographic abnormalities observed in each patient's record are listed in Table V Twelve patients (38 7 per cent)

Table V Electrocardiographic observations other than CAM (total serial electrocardiographic review)

ECG findings	No. of patients		%
Ventricular prematures, multiple or multifocal	20		64 5
Ischemic ST T changes	12		38 7
Left axis deviation	10		32 3
Left atrial enlargement	10		32 3
Left ventricular hypertrophy	9		29 0
A V nodal prematures	9		29 0
Right atrial enlargement	8		25 8
Right ventricular hypertrophy	6		19 4
Old myocardial infarct	*6*		*19 4*
Defective intraventricular conduction	5		16 1
Right bundle branch block	5		16 1
A V block	5		16 1
first degree		3	
second degree		1	
third degree		1	
Isorrhythmic dissociation	2		6 4
Left bundle branch block	1		3 2
Acute myocardial infarct	1		3 2

had ischemic electrocardiographic changes compatible with coronary artery disease, 6 others (19 4 per cent) had electrocardiographic evidence of old myocardial infarction and 1 (3.2 per cent) had evidence of recent infarction A considerable number of patients had conduction abnormalities (right or left bundle branch block, A V block, and defective intraventricular conduction) There was electrocardiographic evidence of left atrial disease in 10 patients (32 per cent) and right atrial disease in 8 (26 per cent)

Arteriosclerotic heart disease and other diseases In addition to the obvious association of this arrhythmia with diabetes mellitus and chronic or acute pulmonary disease, manifestations of arteriosclerotic heart disease were evident in 28 patients (90 per cent) based on clinical electrocardiographic, and autopsy findings. These and other associated disease states are noted in Table VI

Relationship to drugs Clinical records of each patient were carefully examined to determine the relationship of the arrhythmia to cardiac drugs particularly digitalis,

Table VI. Clinical states coexisting with chaotic atrial mechanism in the 31 patients

Disease	No. of patients	%
Arteriosclerotic heart disease	28	90.3
Chronic obstructive pulmonary disease	26	83.9
Diabetes mellitus	23	74.2
Cor pulmonale	17	54.8
Hypertension (B.P. 150/100 or greater)	12	38.7
Urinary tract infection	11	35.5
Azotemia	6	19.4
Acute pulmonary disease (emboli, etc.)	5	16.1
Valvular heart disease	3	9.7
Carcinoma of the lung	2	6.5
Thyrotoxicosis	1	3.2
Multiple myeloma	1	3.2
Guillain-Barré	1	3.2

quinidine, procainamide, diphenylhydantoin and tranquilizers. Eighteen patients (58 per cent) were receiving digitalis when the arrhythmia occurred and, utilizing all available clinical data, digitalis toxicity was strongly suspected in 9 (29 per cent). It should be noted, however, that in other instances CAM occurred while patients were not receiving digitalis and in two instances the arrhythmia ceased upon digitalization and did not recur. Quinidine conversion trial in 3 patients failed to evoke any significant change. Neither a provocative nor a therapeutic effect could be established in scattered instances of the arrhythmia in patients receiving quinidine, procainamide, diphenylhydantoin or various tranquilizers.

Mortality rates. Sixteen of the patients (51.6 per cent) died during hospitalization. This high mortality rate is not surprising when one considers that the patients were elderly individuals with serious cardiac, pulmonary, or other diseases. It is of interest, however, that analysis of the clinical records indicated that 5 of the 16 patients who died (31 per cent) had good clinical evidence of digitalis toxicity. Twelve of the patients who died had CAM at the time of death. Fifteen patients were still living at the end of the study, and of these, 6 had CAM when last observed.

Table VII. Pertinent autopsy findings in 8 of the 16 patients with CAM who died

Autopsy findings	No. of patients	% of autopsied patients
Pulmonary		
Chronic obstructive disease	4	50
Acute purulent bronchitis	2	25
Acute tracheobronchitis	2	25
Acute pulmonary edema	6	75
Pulmonary emboli	1	12.5
Cardiovascular		
Coronary atherosclerosis	8	100
Myocardial infarction, acute	3	37.5
anterolateral	2	
posteroseptal	1	
Myocardial fibrosis	8	100
diffuse	6	
focal	2	
Myocardial hypertrophy	8	100
Ventricular aneurysm	1	12.5
Pericarditis, acute	1	12.5
Papillary muscle fibrosis	5	62.5
Aneurysm, thoracic or abdominal aorta	3	37.5
Pancreas		
Hyalinization of islets of Langerhans	3	37.5
Generalized pancreatic atrophy	2	25
Fatty infiltration	1	12.5
Kidney		
Benign nephrosclerosis	7	87.5
Pyelonephritis	3	37.5
Renal infarct	1	12.5
Thyroid		
Adenoma, benign	4	50

Pathology. Autopsies were performed in 8 (50 per cent) of the 16 patients who died. This study yielded important corroborative information which is condensed in Table VII. Four of the patients (50 per cent) had serious obstructive lung disease. Coronary arteriosclerosis was present in all cases, as was focal or diffuse myocardial fibrosis and various degrees of ventricular hypertrophy. Pathologic changes in the pancreas were found in 6 of the 8 autopsied cases, giving support to the high incidence of diabetes noted clinically. Of interest was

the finding of benign thyroid adenomas in four patients at postmortem examination

Discussion

Little reference to an arrhythmia similar to that described here as chaotic atrial mechanism could be found in the literature Scherf and Schott[3] described several cases of multiform auricular extrasystoles and shifting pacemaker with continual change in the shape of the P wave They agreed with Langeron[4] who indicated that this type of arrhythmia frequently terminated in auricular fibrillation In the present study the arrhythmia ended in atrial fibrillation in only 2 patients, but developed into atrial flutter in 3 patients and paroxysmal atrial tachycardia with A V block in another Considering the age of the patients and the severity of their diseases, it is indeed surprising that more instances of CAM terminating in other atrial arrhythmias did not occur Thus, it seems evident that CAM is frequently a stable autonomous mechanism

Riseman and Segall reported a patient with premature beats from multiple ectopic foci whose electrocardiogram as published apparently displays the arrhythmia herein described In their discussion of this arrhythmia they stated that it was infrequently encountered primarily found in adults with coronary artery disease or systemic infection and that palpitation cough dyspnea chest pain sweating and fainting were the usual symptoms. The findings in the present study are somewhat similar to these but the additional observation of the frequency of associated diabetes mellitus and chronic lung disease must be emphasized In fact, the occurrence was so regular that a syndrome is almost suggested.

Recently Shine and associates reported studies in patients with an arrhythmia termed "multifocal atrial tachycardia. As part of the criteria for diagnosis they listed an atrial rate greater than 100 per minute. Otherwise, the arrhythmia described is entirely similar to the one we describe herein. We prefer the term "chaotic atrial mechanism however since the atrial rate was less than 100 per minute in a number of our cases. The findings of Shine and associates of the arrhythmia relative to elderly age associated pulmonary disease and hazards of digitalis intoxication are similar to ours however these authors made no mention of a high incidence of diabetes.

Chaotic atrial mechanism should not be confused with wandering atrial pacemaker with fairly fixed P R intervals nor with a pacemaker apparently wandering into the A V node In these a certain rhythmic pattern can usually be established In CAM however there is a completely random and chaotic impulse formation apparently from multiple ectopic areas in the atria CAM is frequently preceded and followed by multiple atrial premature systoles but is distinguished from them in that no single atrial focus acts as the fundamental atrial pacemaker

In chaotic atrial mechanism one could postulate that no single dominant pacemaker is present for one or more reasons, and multiple hyperexcitable ectopic foci vie for control. In some instances, multiple simultaneous parasystolic foci may be active. In others, aberration in conduction of impulses through the atrial muscle may appear to represent multiple ectopic foci

Ischemia or injury to the sinus node with diminution of normal sinus node dominance of the heart probably plays a major role in the genesis of this arrhythmia This seems to be true for atrial arrhythmias occurring in acute myocardial infarction. Ample evidence of coronary artery disease was present in the group under study All of the autopsied patients exhibited significant coronary arteriosclerosis and myocardial fibrosis.

Extranodal atrial injury and atrial distension have also been postulated as factors in the etiology of atrial arrhythmias. One might assume that if fibrosis existed in the ventricle of all 8 autopsied patients, the atria might be similarly affected also. To date detailed histologic studies of the atria and conduction system have not been carried out.

In view of the above factors it is tempting to try to reconcile the frequent association of diabetes mellitus and chronic pulmonary disease to the pathophysiology of CAM It may be that through small vessel disease associated with diabetes ischemia

of the nodal and intra-atrial conduction tissue occurs and that chronic lung disease with some degree of pulmonary hypertension produces the necessary distension or stress of the right atrium

Digitalis may play a role in the genesis of the arrhythmia in a few instances, but its total relationship is not entirely clear at the present time. Eighteen (58 per cent) of the patients were receiving digitalis when the arrhythmia occurred but further data are needed before any causal relationship can be established

Digitalis toxicity occurs frequently in patients with cor pulmonale.[9] Because of pulmonary insufficiency dyspnea, and the usual rapid heart rate in patients of the type under study there is a tendency to increase digitalis dosage excessively In addition most of the patients are elderly in heart failure, and are often receiving diuretics. All of these factors tend to predispose to digitalis intoxication.

Most probably a number of factors are of pathophysiologic importance in the genesis of CAM but regardless of the etiology the ultimate prognosis is poor As stated there was a 52 per cent hospital mortality rate (16 deaths) in those patients who had CAM during their hospital stay and 12 patients died with the arrhythmia apparently continuing to the moment of death It is probable that the fast heart rate associated with CAM resulted in onset or propagation of heart failure. The irregularity of the rhythm would further impair cardiac contractibility cardiac output, and myocardial efficiency

The best therapeutic approach to CAM appears to be treatment of the underlying disease processes. As noted by Shine and associates,[8] bronchodilator sympathomimetic drugs may contribute to a fast cardiac rate in a number of the patients. If excess digitalis is suspected the drug should be withheld Quinidine, procainamide, and diphenylhydantoin did not appear to be helpful in the few instances in which they were given. In those cases in which digitalization was followed by cessation of the arrhythmia it is assumed that improvement in the cardiopulmonary status of the patient or removal of inciting circumstances contributed to the termination of the rhythm disturbance. Increasing digitalis dosage in an attempt to control the heart rate in CAM appeared to be hazardous. Electric cardioversion has not been attempted

Summary

A distinctive sustained atrial arrhythmia characterized by chaotic and random atrial activity with at least three different types of P' waves in a single electrocardiographic lead and variability of the P P R R and P R intervals, has been described in 31 patients. This disturbance has been named chaotic atrial mechanism (CAM) In the majority of patients, the cardiac (atrial and ventricular) rate with this rhythm disturbance ranged from 100 to 150 beats per minute, but in rare instances it was as low as 56 or as fast as 200 beats per minute. On physical examination it was usually indistinguishable from atrial fibrillation. The average age of the patients was 68.5 years. Such a striking correlation with pulmonary disease (83 9 per cent) and with diabetes mellitus (74 2 per cent) occurred that a syndrome was almost suggested

Probable important factors in the pathogenesis of the arrhythmia are diffuse atrial disease (ischemia, fibrosis, distension stress) and damage to the sinus node with disorderly competition for pacemaker control by other foci of atrial pacemaker tissue. In support of this premature atrial beats were noted either before the onset of the arrhythmia or after its termination, in 61.3 per cent of the patients studied.

In the majority of patients the arrhythmia lasted less than two weeks. The shortest apparent sustained duration was several seconds and the longest six years. The best therapeutic approach appeared to be that directed toward any underlying pathologic condition especially pulmonary disease, diabetes mellitus, congestive heart failure, and infection Antiarrhythmic drugs did not prove effective at safe dosage levels in the instances in which they were tried. Direct current cardioversion has not been attempted. Response to digitalis was variable and unpredictable, and intoxication frequently occurred when high dosages were used in an attempt to control cardiac rate.

The potentially grave prognosis in pa-

tients with this rhythm disturbance is underscored by the fact that 16 of the 31 patients (52 per cent) died during the hospital stay in which the arrhythmia occurred and that 9 of these died within 45 days of its onset. Twelve of those who died apparently had the arrhythmia at the time of death

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Electrocardiographic diagnosis of malformations associated with tricuspid atresia
Correlation with morphologic features

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While the typical electrocardiographic pattern of tricuspid atresia consisting of left axis deviation and counterclockwise loop rotation in the frontal plane has been known since 1936,[1] it was only more recently noted that some features of the electrocardiogram (ECG) in tricuspid atresia are related to the type of the associated malformation.[2-4] It has been stated that a normal or rightward-oriented frontal QRS axis may occur in tricuspid atresia if the great vessels are transposed.[2-4] This study is an attempt to correlate electrocardiographic features in tricuspid atresia with the presence or absence of subpulmonary stenosis. Recent morphologic studies indicate that the presence or absence of subpulmonary stenosis and the size of the right ventricle in tricuspid atresia are determined by the size of the ventricular septal defect.[5] When the ventricular septal defect is small, subpulmonary stenosis and a small right ventricle exist. The best differentiation among the anatomic subtypes of tricuspid atresia was found to result from vectorial analysis of the ECG.

Materials and methods

Scalar ECG's from 31 patients with tricuspid atresia were available for review. The diagnosis was verified by autopsy in 14 cases and by cardiac catheterization and angiocardiography in 17.

The ECG's were evaluated by the usual criteria, and the precordial leads of the scalar electrocardiograms were used for vectorial analysis in which a horizontal vector loop was constructed (Fig. 1).

Morphologic findings

These comments pertain to the 14 autopsies. No remnant of the tricuspid valve was present in the floor of the enlarged right atrium. A "dimple" (a tiny endocardium-lined blind pocket) was identified anterior and to the left of the ostium of the coronary sinus in 9 of the 14 cases. The dimple marked the location of the central fibrous

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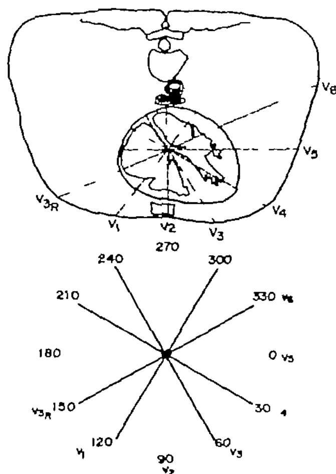


Fig. 1 Precordial electrocardiographic leads used for construction of horizontal vector loop.

body The membranous septum was abnormal it was absent in 12 cases and diminutive in 2. Thus, the regions in which major atrioventricular conduction tissue would be expected to be located were abnormal.

Ten of the 14 specimens were examples of type I tricuspid atresia in which the great arteries are normally related There was pulmonary atresia (type Ia) in 1 subpulmonary stenosis (type Ib) in 8 and no obstruction to pulmonary blood flow (type Ic) in 1 In all 10 the right ventricle was a small chamber of variable size. It was a tiny endocardium lined muscular chamber in the one example in which the pulmonary valve was atretic (type Ia) no ventricular septal defect (VSD) was present in this heart. In the eight cases of type Ib the right ventricle was a small elongated chamber which lay obliquely along the base of the heart and had a diameter the same as that of the pulmonary artery The site of obstruction to blood flow was the narrow tubular-shaped VSD Neither valvular nor infundibular pulmonary stenosis in the usual sense was present. The one specimen of type Ic had the largest right ventricle of any of the type I hearts, and the VSD was large. In these hearts, therefore the size of the right ventricle was related directly to the size of the VSD

Four of the hearts had transposition of the great arteries (type II) [7] In one subpulmonary stenosis (type IIa) was due to a muscular band in the left ventricle No obstruction to pulmonary blood flow was present in the three other hearts (type IIb) In all four the transposition was of the dextro variety[8] (the aorta was situated

anterior and to the right of the pulmonary trunk at the base of the heart) As in the examples of type I tricuspid atresia the size of the right ventricle was related to the size of the VSD and it was larger in these hearts than in any of the hearts without transposition of the great arteries.

Electrocardiographic findings

Disorders of rhythm Atrial fibrillation and flutter were seen in a 45-year-old patient who had normally related great vessels and no pulmonary stenosis (type Ic) Occasional premature ventricular contractions were observed in a baby with type Ib tricuspid atresia (subpulmonary stenosis but no transposition of the great vessels) All the other patients had normal sinus rhythm

P wave Right atrial hypertrophy manifested by peaked or diphasic P waves higher than 2.5 mm in Lead I II or V_1, was present in 19 of the 31 cases (Table I). All morphologic varieties of tricuspid atresia were included in these 19 cases. Left atrial hypertrophy evidenced by broad P waves with notching in Lead I or V_1 or with a diphasic or inverted pattern in Lead V_1 was diagnosed in three cases, all type Ic morphologically Biatrial hypertrophy manifested by a combination of these ca-teria was found in three cases two were type Ib and one was type IIa. The height of the P waves in the ECG was not related to the difference between the mean pressures in the right and left atria or to the peak systolic pressure in the right atrium.

QRS complex

STANDARD AND UNIPOLAR EXTREMITY

Table I P wave analysis in scalar ECG's in 31 cases of tricuspid atresia

Atrial enlargement	No. of cases					Total
	Type of tricuspid atresia					
	I	Ib	I	II	IIb	
Right	2	9	4	2	2	19
Left	0	0	3	0	0	3
Biatrial	0	2	0	1	0	3
None	1	3	0	1	1	6
Total	3	14	7	4	3	31

Table II Analysis of QRS complexes in scalar precordial ECG's in 29 cases of tricuspid atresia

QRS complexes	No. of cases					Total
	Type of tricuspid atresia					
	I	Ib	Ic	II	IIb	
Left ventricular hypertrophy						15
By voltage criteria	0	6	3	3	3	
By prolonged intrinsicoid deflection in V	1	2	0	0	0	3
Normal precordial QRS complexes	2	5	4	0	0	11
Total	3	13	7	3	3	29

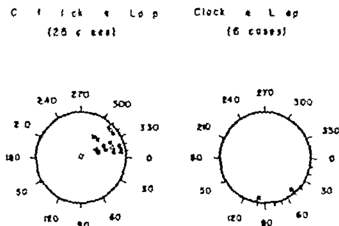


Fig 2 Maximal QRS axis in frontal plane in tricuspid atresia None of six cases with clockwise loops had left axis deviation for age (right). Case with counterclockwise loop in frontal plane and no left axis deviation was subgroup IIa of tricuspid atresia (transposition and pulmonary stenosis) and was associated with isolated dextrocardia (left, mean QRS axis +60°). Symbols Circles type I—with spurs, I open Ib solid, I triangles type II—open, IIa, solid, IIb.

LEADS. The mean QRS axis and the loop rotation found in these 31 cases are shown in Fig 2 The classic ECG of tricuspid atresia is characterized by left axis deviation and a counterclockwise loop (Fig 3) Among the 24 cases which presented this pattern all anatomic types were present without predilection for any specific type. Seven cases did not have left axis deviation and six of these had clockwise frontal loops. Transposition of the great arteries[3,4] was present in three of these seven cases and pulmonary atresia in one[3,4] The remaining three cases were type Ib (subpulmonary stenosis but no transposition of the great vessels) (Fig 4)

PRECORDIAL LEADS Twenty-nine precordial ECG s were evaluated. The diagnosis of left ventricular hypertrophy was based on the following criteria (1) voltage in (RV-6 + SV 1) > 40 mm. or RV-6 > 26 mm. or SV 1 > 4 mm. (2) prolonged intrinsecoid deflection in Lead V_6 (>0 04 sec. in patients less than 16 years old >0.05 sec. in patients more than 16 years old) and (3) deep Q waves in Lead V_6 (>4 mm.) (Table II) Left ventricular hypertrophy was indicated by voltage criteria in 15 cases and by a prolonged intrinsecoid deflection in Lead V in 3 cases. Precordial ECG s were normal in 11 cases, none of which included transposition of the great vessels.

Vectorial analysis of the precordial

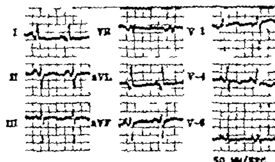


Fig 3 ECG in type Ib tricuspid atresia (pulmonary stenosis but no transposition of great arteries) in 1-month-old infant Note left axis deviation (300°) and counterclockwise loop rotation in frontal plane.

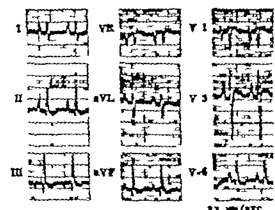


Fig 4 ECG in type Ib tricuspid atresia (pulmonary stenosis but no transposition of great arteries) in 10-month-old infant. Note normal QRS axis (0°) and clockwise loop rotation in frontal plane.

Table III. Vectorial analysis of scalar precordial ECG's in 29 cases of tricuspid atresia

Horizontal QRS loop	*No. of cases*					*Total*
	Type of tricuspid atresia					
	Ia	*Ib*	*Ic*	*II*	*IIb*	
Rotation of horizontal QRS loop						
Counterclockwise	3	13	7	2	3	28
Figure eight	0	0	0	1	0	1
Maximal axis of horizontal QRS loop						
270° to 360°	2	11	6	1	1	21
180° to 270°	1	1	1	1	0	4
0° to 90°	0	1	0	1	1	3
Wide horizontal QRS loop	0	2	4	0	3	9
Narrow horizontal QRS loop	3	11	3	3	0	20
Direction of initial horizontal QRS vector						
Right anteriorly	0	5	7	1	1	14
Right posteriorly	0	0	0	1	0	1
Left anteriorly	3	8	0	1	2	14

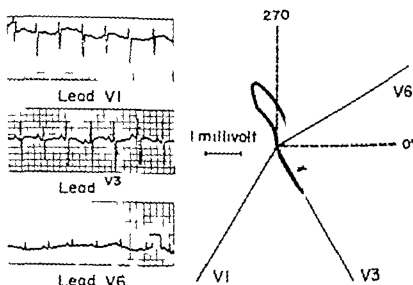


Fig. 5. Vectorial analysis of precordial ECG in type Ib tricuspid atresia (pulmonary stenosis but no transposition of great arteries). Typical narrow loop; patient 1 month old.

ECG's was possible in 29 cases (Table III). Twenty-two (76 per cent) had the characteristic features of the horizontal vector loop in tricuspid atresia. These features were a posteriorly oriented maximal QRS axis between 270 and 360 degrees and a counterclockwise loop. In four cases the maximal QRS axis was between 120 and 270 degrees and in three instances it was between 0 and 90 degrees. The shape of the horizontal vector loop was related to the anatomic type. Of the 20 cases in which it was narrow and elongated (Fig. 5) pulmonary atresia or stenosis was present in 17, while of the 9 cases with wide horizontal loops (Fig. 6) pulmonary stenosis was

Table IV. T wave analysis in scalar precordial ECG's in 29 cases of tricuspid atresia

T waves	No. of cases					
	Type of tricuspid atresia					Total
	I	Ib	Ic	II	IIb	
T in V						
Tall, peaked, and upright	1	2	1	1	1	6
Biphasic	1	6	0	0	0	7
Inverted	0	0	4	0	2	6
Normal	1	5	2	2	0	10
Total	*3*	*13*	*7*	*3*	*3*	*29*
T in V associated with inverted or biphasic waves in V						
Upright	0	4	4	0	1	9
Biphasic	1	2	0	0	1	4

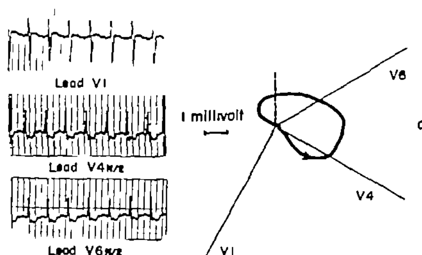


Fig. 6. Vectorial analysis in type Ic tricuspid atresia (no transposition or pulmonary stenosis). Typical wide loop patient 1 month old.

present in only 2. In 12 of the 20 cases with narrow loops the initial vector was directed toward the left and anteriorly.

T waves. In the precordial ECG's, tall peaked upright T waves were noted in V in six cases with no apparent correlation with the anatomic type of tricuspid atresia or with pulmonary flow (Table IV). Inverted T waves in V_6 were present in six cases, none of which included pulmonary stenosis. Biphasic T waves in V_6 were noted in an additional seven cases and in general the T waves in the right precordial lead (V_1) were reciprocally upright or biphasic in those patients with inverted or biphasic T waves in V_6.

Discussion

The typical electrocardiographic pattern of tricuspid atresia [1,2] consisting of left axis deviation and counterclockwise QRS rotation in the frontal plane, was present in 24 of the 31 patients (77 per cent) Frequent occurrence of left axis deviation in tricuspid atresia was first noted in 1936 [1] Recently two hypotheses have been proposed to explain the left axis deviation in the frontal plane in tricuspid atresia These are congenital fibrosis of the left bundle branch[10] and abnormalities in the peripheral portions of the conduction system of the left ventricle [4] Another possibility is that morphologic abnormalities exist in the proximal portion of the atrioventricular conduction system because in specimens from cases of tricuspid atresia reviewed in this study the membranous septum was absent in 12 of 14 cases and rudimentary in 2

Among the seven cases (23 per cent) without left axis deviation the QRS axis was either normal (six cases) or deviated to the right (one case) These six cases included three instances of transposition of the great arteries (Fig 2) If tricuspid atresia is associated with transposition of the great arteries, a normal or rightward oriented electrical axis may be as common as left axis deviation [1-4] The right ventricle is larger in patients with transposition of the great vessels than in those with tricuspid atresia with normally related great vessels which may contribute significantly to the presence of increased right ventricular potentials. Cabrera and associates[11] described a counterclockwise rotation of the frontal plane loop as the second most characteristic finding in tricuspid atresia. This study suggests that a counterclockwise inscription of the frontal loop in tricuspid atresia occurs only in the presence of left axis deviation and that in cases with a normal or rightward axis the loop rotation is clockwise (Fig 2) In the presence of a normal frontal QRS axis in tricuspid atresia counterclockwise loop rotation might be anticipated only in older children because this finding is frequently associated with advancing age.

Precordial ECGs in tricuspid atresia fulfilled the criteria based on voltage and intrinsicoid deflection for left ventricular hypertrophy in 18 of 31 cases (58 per cent) All cases of left ventricular hypertrophy occurred with type I tricuspid atresia (normal relationship of great vessels). Because the right ventricle tends to be smaller in type I tricuspid atresia than in type II (transposition of great vessels),[1] increased left ventricular complexes may be displayed unopposed in the former while they are balanced by right ventricular potentials in the latter

The horizontal vector loop constructed from the precordial ECG was oriented posteriorly and to the left with a predominantly counterclockwise inscription. Vectorial analysis of scalar electrocardiograms was used for vectorial evaluation in this study because since 1920[12] it has been applied to the interpretation of electrical events and makes use of a lead system which has not been significantly changed. The value of the method was re-emphasized by the recent monograph by Goldberger[3] The configuration of the horizontal QRS loop in tricuspid atresia found in this study was similar in general to the horizontal vector loops reproduced with the system of Frank[4,6] and the cube system [11] While a predominantly clockwise inscription of the horizontal QRS loop has also been reported in tricuspid atresia studied with the cube system [11] a counterclockwise rotation prevails in Frank vectorcardiograms.[13] Since the horizontal vector loops in tricuspid atresia are narrow in most instances with the major projection near the anteroposterior axis differences between the various lead systems which are most pronounced for the anteroposterior axis in the horizontal plane, may induce differences in the direction of rotation.

In this study the shape of the horizontal vector loop was related to the anatomic type of tricuspid atresia in that the loop was narrow elongated and oriented more posteriorly in 17 of the 19 patients with pulmonary stenosis (Fig 5) and wide and more anteriorly placed in 7 of the 10 without pulmonary stenosis (Fig 6) In tricuspid atresia without pulmonary stenosis, the initial horizontal forces in the anterior direction may be increased because of the increased blood volume which reaches the right ventricle in the absence of obstruction to pulmonary flow According to Schwan and Kay [4] the conductivity of the intra-

cavitary blood mass is nearly 10 times that of surrounding tissue. This would tend to short-circuit tangential electrical forces generated by the myocardium and increase forces having a radial direction. The anterior position of the right ventricle as observed[4] in heart specimens of tricuspid atresia without pulmonary stenosis could thus well explain the increase in anterior rather than rightward forces generated by an increased right ventricular blood volume.

In Lead V_6, biphasic or inverted T waves were found as frequently as normal T waves (Table IV). Inverted T waves in V_6 occurred only in patients who had tricuspid atresia without pulmonary stenosis. When associated with large left-to-right shunts (pulmonary to systemic flow ratio greater than 2.5), this T wave change was more frequently present in this study in tricuspid atresia than in other congenital heart defects. The occurrence of these abnormal T wave patterns (inverted or biphasic in V_6) which often are considered to indicate left ventricular "strain" or systolic or pressure overloading is an interesting finding in tricuspid atresia because all these patients had normal left ventricular systolic pressure and increased chamber volume, features which should be associated with diastolic or volume overloading of the left ventricle according to Cabrera and Monroy.[14] In tricuspid atresia, as in some other congenital cardiac malformations, these repolarization abnormalities do not correlate well with the systolic and diastolic overload concept, presumably because myocardial repolarization is dependent not only on factors which influence myocardial oxygenation, such as intramural ventricular pressure, but also on the sequence of cardiac excitation.[5] Differences in T wave patterns in tricuspid atresia with or without subpulmonary stenosis could be due to variation in the sequence of excitation observed in the horizontal vector loop. This suggestion is also compatible with the observation by Burch and DePasquale[3] that the ventricular gradient in tricuspid atresia may vary with the presence or absence of pulmonary stenosis.

Right atrial hypertrophy occurred in 19 of the 31 cases (61 per cent). Although it has been suggested previously that in tricuspid atresia the height of the P wave is related to the peak systolic pressure in the right atrium, in this study the size of the P wave was not related to the difference between the mean pressures in both atria nor to the peak systolic pressure in the right atrium. In Gamboa and associates' recent report there was no correlation between the height of the P wave and the peak right atrial pressure, while Ferguson and associates[17] noted a "rough correlation" between the heights of the right atrial *a* wave and P wave. In our study, right atrial hypertrophy was most frequent in those patients with high systemic blood flows per unit surface area. This would suggest that in tricuspid atresia the size of the P wave reflects volume rather than pressure overloading of the right atrium. Left atrial hypertrophy occurred in 3 of 31 cases (10 per cent). It was most likely related to an increased size of the left atrium because in all three patients, pulmonary blood flow was increased and left atrial pressures were normal. Burch and DePasquale[3] have indicated that in tricuspid atresia biphasic P waves in Lead V do not necessarily indicate the presence of left atrial enlargement because they may be due to an extreme dilatation of the right atrium. P wave patterns previously described in tricuspid atresia such as "P tricuspidale"[4] and a leftward shift of the P axis[3] in the frontal plane beyond +60 degrees were also found in this study. P-tricuspidale was present in less than half of the cases and a leftward shift of the P axis was found in more than half of the cases.

Summary

The electrocardiographic findings in 31 cases of tricuspid atresia were reviewed. Electrocardiographic differentiation of the types of tricuspid atresia was possible to some extent but vectorial analysis of the scalar ECG's suggests that the vectorcardiogram provides the best and easiest differentiation among the anatomic types of tricuspid atresia. Patients with transposition of the great vessels (type II) tended to have no left axis deviation (as previously reported) and a clockwise rotation of the vector loop in the frontal plane. In the precordial ECG's, left ventricular hypertrophy based on voltage criteria was

absent when the great vessels were transposed Vectorial analysis of precordial scalar ECG s showed that patients without pulmonary stenosis or atresia tended to have wide horizontal vector loops with display of anterior forces and those with pulmonary stenosis frequently had narrow horizontal loops which were oriented posteriorly Repolarization abnormalities such as inverted or biphasic T waves in V_6 were present only in patients with increased pulmonary flow The electrocardiographic features observed with various associated *malformations of tricuspid atresia* appeared to be related to the morphologic findings in these malformations.

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Treatment of cardiac arrhythmias with phentolamine

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In his experimental work on dogs, Leimdorfer[1,2] in 1952 demonstrated that the administration of phentolamine prevented nicotine sulfate and epinephrine-induced arrhythmias and converted methachol neinduced atrial flutter fibrillation and atrioventricular nodal rhythm to normal sinus rhythm. He further showed that phentolamine administration prevented the appearance of pronounced bradycardia during electrical stimulation of the vagus nerve. He concluded that phentolamine had the property to revert the abnormal heart rhythm to normal by inducing again the predominance of the normal pacemaker in the sinoatrial node. However, he did not elaborate any further on its mode of action nor did he advocate its use in the treatment of cardiac arrhythmias in man. Except for one reported observation, to the best of our knowledge no other attempts have been made to treat cardiac arrhythmias with this agent in man, mainly because the experience with the 5 mg. dose used as a screening test for pheochromocytoma showed that the drug could produce severe hypotension and an alarming tachycardia.

We recently observed that the continuous intravenous administration of .3 mg. per minute of phentolamine to patients in congestive heart failure led to a marked improvement in left ventricular function.[3] If ventricular premature contractions were present in these patients prior to the administration of the drug, they would either diminish in number or disappear by the end of the study. In an additional study 10 normal dogs were rapidly digitalized with ouabain until electrocardiographic abnormalities of rhythm occurred. Phentolamine infused at 3 mg. per minute rapidly abolished ventricular tachycardia in 4 of 5 cases, ventricular premature contractions in 3 cases, and complete heart block in 1 case, and it increased the rate in 1 case of sinus bradycardia. These observations led us to consider the use of phentolamine as an antiarrhythmic agent.

In the present paper we report our experience with the use of phentolamine in patients with various cardiac arrhythmias.

Methods

Forty-three patients with cardiac disease and arrhythmias, observed on the electrocardiogram, were selected for treatment

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with phentolamine. In some of the patients it was believed that the arrhythmia was directly due to an overdose of digitalis, while in other patients digitalis either played no role or an uncertain role.

All patients were at complete bed rest before the trial. A 60 second control tracing of the basic rhythm was recorded. Then .3 mg per minute of phentolamine was given intravenously for 15 minutes. This was accomplished by placing 3 ampules or 15 mg of phentolamine in 200 c.c. of glucose and water The resultant mixture was infused at a rate of 60 drops per minute into the antecubital vein The effect of phentolamine on these arrhythmias was monitored electrocardiographically during and ten minutes after the infusion of the drug no effort was made to observe the duration of this effect beyond this period.

Results

Ventricular premature contractions.

CLINICAL MATERIAL. Eleven patients had frequent ventricular premature contractions due to digitalis toxicity Fourteen patients with ventricular premature contractions were not on digitalis.

RESULTS In the digitalis-induced group the extrasystoles were abolished in 1 patient (Fig 1) unaffected in 1 patient, and their frequency markedly diminished in the

Table I Frequency of ventricular premature contractions (V.P C) due to digitalis toxicity

Patient No	Control observation frequency of V.P C	Control sinus rate (beats/min.)	During phentolamine infusion frequency of V.P C.	Treatment sinus rate (beats/min.)	When effect was observed (min.)
1	Every other beat		None	100	5
2	12 per minute	85	3 per minute	83	1
3	Every other beat		Every fourth beat	85	5
4	Every other beat		18 per minute	90	
5	60 per minute	85	2 per min te	95	5
6	E ery other beat		Every other beat		
7	18 per minute	80	2 per minute	80	5
8	30 per minute	85	15 per minute	95	7
9	Every third beat	90	3 per minute	95	15
10	28 per minute	100	12 per minute	100	10
11	9 per minute	100	1 per minute	100	10

Table II Frequency of ventricular premature contractions in patients not on digitalis

Patient No	Control observation frequency of V.P C	Control sinus rate (beats/min.)	During phentolamine infusion frequency of V.P C.	Treatment sinus rate (beats/min.)	When effect was observed (min.)
1	Every other beat		None	65	6
2	45 per minute	100	None	100	8
3	Every third beat	65	None	60	14
4	Every other beat		Every fourth beat	95	11
5	E ery third beat	70	10 per minute	80	7
6	17 per minute	90	3 per minute	90	7
7	80 per minute	100	15 per minute	105	8
8	24 per min te	95	3 per minute	95	8
9	Every fourth beat	80	2 per minute	75	8
10	36 per minute	90	2 per minute	90	10
11	24 per minute	105	16 per minute	100	10
12	40 per minute	95	24 per minute	100	10
13	Every third beat	110	None	90	10
14	9 per minute	75	2 per mi ute	80	10

other 9 patients. In the patients not on digitalis, the extrasystoles were abolished in 4 patients and markedly diminished in the remaining patients. The frequency of the premature contractions prior to and during therapy are listed in Tables I and II

Third degree heart block

CLINICAL MATERIAL. Three patients, not on digitalis, with complete heart block were treated

RESULTS. The first patient recently developed arrhythmia (few hours duration) and with treatment reverted to sinus rhythm (Fig 2) He remained in sinus rhythm for 2 days and then developed a 2 1 A V block which also reverted to sinus rhythm with phentolamine administration (Fig 3) The other 2 patients with complete heart block of a few years duration did not respond to treatment.

Second degree heart block

CLINICAL MATERIAL. Four patients were in this group

RESULTS One patient with a 2 1 A V block of many years duration did not respond to treatment. The second patient, with a Wenckebach phenomenon due to digitalis toxicity reverted to sinus rhythm with treatment (Fig 4) The third patient

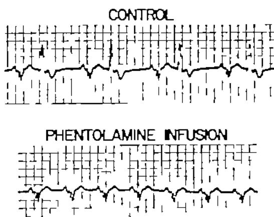


Fig 1 Elimination of ventricular premature contractions due to digitalis by phentolamine infusion.

CONTROL

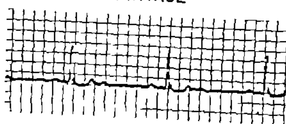
PHENTOLAMINE INFUSION

CONTINUOUS RECORDING 10 MINUTES OF PHENTOLAMINE

12 MINUTE RECORDING

Fig. 2 Conversion of complete heart block to sinus rhythm by intravenous phentolamine.

acutely developed a left bundle branch block and a Wenckebach phenomenon as a result of an acute myocardial infarction Phentolamine did not affect the arrhythmia or the conduction defect. The last patient with a digitalis-induced Wenckebach phenomenon reverted to a first degree heart block with therapy No patient studied had a Mobitz type II block The small group of patients studied does not permit a precise analysis on the effect of phentolamine on A V conduction



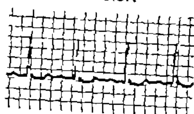


Fig 3 Conversion of 2 1 A V block t sinus rhythm by intravenous phentolamine

Atrial flutter

CLINICAL MATERIAL. Four patients had atrial flutter

RESULTS No patient reverted to sinus rhythm or demonstrated a slowing of the ventricular rate.

Atrial fibrillation

CLINICAL MATERIAL. Treatment was given to 6 patients with atrial fibrillation. Three of the patients were receiving digoxin.

RESULTS No effect was observed on the electrocardiogram

Paroxysmal atrial tachycardia

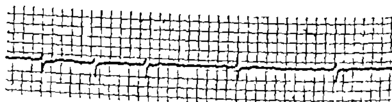
CLINICAL MATERIAL. One patient, not on digitalis was treated with phentolamine.

RESULTS No effect was observed on the electrocardiogram

There were no side effects associated with the administration of the drug. With the dose of phentolamine employed a decrease in the blood pressure did not occur

Discussion

In a recent work from our laboratory[13] phentolamine was administered intravenously for 20 minutes at a rate of 0.5 mg per minute to 13 patients with abnormal left ventricles, who had previously been in left ventricular failure. In these patients phentolamine produced an increase in the cardiac output systemic pressure cardiac rate and left ventricular dp/dt, and a fall in the pulmonary artery pressure systemic peripheral resistance, left ventricular end-diastolic pressure and left ventricular end-



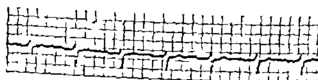


Fig 4 Wenckebach phenomenon reverted t sinus rhythm with phentolamine infusion.

diastolic volume. Administration of the drug produced no untoward side effects. In addition we have recently administered phentolamine intravenously up to 90 minutes, to 6 patients with cardiac disease undergoing diagnostic cardiac catheterization. The favorable hemodynamic results were maintained during the infusion and the lack of side effects was again verified.

This improvement in cardiac function may be explained by the recent observations of Dairman and his associates. They administered phentolamine (5 mg per kilogram) to rats. At the height of receptor blockade the conversion of a tracer dose of tyrosine-^{14}C to norepinephrine in heart, brain and adrenals was increased threefold with no alteration in specific activity of tyrosine in blood and tissues. From these studies Dairman concluded that receptor blockade led to increased synthesis and release of norepinephrine in the three organs that were measured.

Phentolamine was effective in abolishing or decreasing the number of ventricular extrasystoles in patients not on digitalis. This was not surprising in view of our previous observation that phentolamine could improve left ventricular function. However this explanation might be an oversimplification of the drugs antiarrhythmic action in failure patients and other factors may be involved.

A similar favorable effect was also observed in patients with ventricular extrasystoles due to digitalis. This was an unexpected finding and undoubtedly involves some other mechanism of action the exact nature of which remains to be elucidated. It is difficult to envision how an increased production of catecholamines could suppress arrhythmias induced by digitalis. It would have been of great clinical interest to administer phentolamine to patients with ventricular tachycardia. However the opportunity did not present itself.

Phentolamine was not effective in the treatment of second or third degree heart block of long duration. However when the block was of recent onset then a favorable result could occur. The remarkable establishment of regular sinus rhythm in the patient with complete heart block of recent onset may have been due to the improvement in left ventricular function.

Obviously a larger series of patients in complete heart block will be required to substantiate this interesting observation. Further additional patients should be studied in order to ascertain the effect of phentolamine on A-V transmission. Phentolamine was ineffective in controlling the fast ventricular rate of atrial fibrillation and atrial flutter. It would appear that the drug should not be used in these two conditions; however the small group of patients studied makes these conclusions tentative.

Phentolamine administered at a rate of 0.3 mg per minute proved to be rapid in action and devoid of side effects. The results obtained in this series of patients indicate that phentolamine may be of great clinical value as an antiarrhythmic agent, especially in the treatment of ventricular premature contractions.

Summary

Clinical experience with the use of phentolamine in the management of a variety of cardiac arrhythmias is described. Phentolamine is valuable in reducing or abolishing digitalis or nondigitalis-induced ventricular extrasystoles. It may prove valuable in treating second or three degree heart block of recent onset. These studies indicate that phentolamine warrants further study as an antiarrhythmic agent.

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The diagnostic value of the atrial gallop in acute myocardial infarction

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The audible atrial gallop is a sound produced in the ventricle during the ventricular filling associated with atrial contraction.[1,2] An atrial gallop occurs when there is hypertrophy of ventricular muscle and diminished ventricular distensibility. It is frequently present in patients with hypertension, aortic stenosis, myocardiopathies, and coronary artery disease.[3-9] An atrial gallop may also be present when there is increased ventricular filling with normal ventricular compliance such as occurs in patients with severe anemia, thyrotoxicosis, or a peripheral arteriovenous fistula.[10-12] An atrial sound frequently accompanies delayed atrioventricular conduction even in the absence of clinically detectable heart disease.[13,14]

The ventricular gallop is a sound produced in the ventricle in early diastole during passive rapid filling.[15-17] It is a frequent finding in normal children and young adults and in patients with high cardiac output.[15,16-17] However, the presence of a ventricular gallop in patients over the age of forty usually indicates either myocardial decompensation or A-V valve incompetence.[14,1]

In patients with acute myocardial infarction, the reported frequency of gallop rhythm is quite variable.[18,19] The purpose of this study is to determine the incidence of atrial and ventricular gallops during acute infarction by serial auscultation and phonocardiograms, and to define their diagnostic value in separating patients with myocardial infarction from those with chest pain of other etiology.

Methods

Fifty consecutive patients admitted to a coronary care unit were evaluated with serial auscultation and phonocardiography. The group consisted of 39 men and 11 women who presented with a history of chest pain and were in sinus rhythm.

Twenty patients had acute myocardial infarction. The diagnosis was based on clinical evaluation as well as serial electrocardiograms and determinations of serum creatine phosphokinase, serum glutamic oxaloacetic transaminase, and lactic acid dehydrogenase.

Simultaneous apical phonocardiogram, apexcardiogram and Lead II electrocardiogram were recorded on each patient at the

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time of admission and daily while they were in the coronary care unit. Similar records were obtained weekly during the remainder of the patients hospitalization and at two week or monthly intervals in 30 of the patients following discharge.

An additional 87 patients with acute myocardial infarction were followed daily with auscultation by the same observer (R. O R.) and each patient had at least one phonocardiogram recorded during hospitalization to substantiate the ausculta tory findings.

Phonocardiograms were recorded with a Rochelle salt crystal microphone (Shure Brothers Model R7) having a linear response from 50 to 1,000 cycles per second. The apexcardiogram used for timing pur poses was obtained with the same 5 cm. diameter bell connected by rubber tubing to an enclosed diaphragm (piezoelectric effect) Recordings were made at the end of a normal expiration with the patient in the left lateral position. The phonocardiograms were recorded at a paper speed of 75 mm per second, with a filter slope of 24 decibels per octave and both with attenuation of frequencies below 50 and 100 cycles per second to check the audibility of the sounds recorded. Initial tracings were recorded with either a Sanborn twin beam photographic apparatus or a Hewlett Packard 350-1700C heart sound preamplifier with a 4360 polybeam recorder Subsequent recordings were made with the latter instru ment, and a four channel Hewlett Packard oscilloscope was used to observe the param eters to be recorded An atrial gallop was identified on the tracings as a low frequency sound coincident with the presystolic "a wave of the apexcardiogram and beginning before the QRS complex of the simulta neous electrocardiogram (Fig 1) A sound with similar phonocardiographic configura tion also coincident with the "a wave but following the onset of the QRS complex is termed an atrial component of the first sound[18] (Fig 2) A ventricular gallop is defined as a low frequency sound occurring 0.12 to 0.20 sec. after the aortic component of the second sound and synchronous with the peak of the rapid filling wave of the apexcardiogram (Fig 1) All atrial gallops atrial components, and ventricular gallops recorded in this study were audible, and

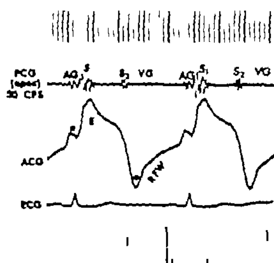


Fig 1 Simultaneous apical phonocardiogram (*PCG*), apexcardiogram (*ACG*) and Lead II electrocardiogram (*ECG*) recorded on a 52 year-old man with acute myocardial infarction. On *PCG* *AG* Atrial gallop *VG* ventricular gallop On *ACG* presystolic wave *E*, systolic ejection phase *O* opening of mitral valve *RFW* rapid filling wave. Time lines are 0 04 sec apart.

frequently the presystolic and rapid filling wa es of the apexcardiogram were visible and palpable

Results

The 50 patients followed with serial phonocardiograms may be divided into three groups as shown in Table I All of the 20 patients diagnosed as having acute myocardial infarction on the basis of appropriat electrocardiogram and serum enzyme changes had atrial gallops at the time of admission (Fig 3) In addition 13 patients had ventricular gallops. Follow up period n this group ranged from four weeks to six months and averaged three months. In 7 patients the atrial gallop moved toward the first heart sound to become an atrial com ponent on phonocardiogram (Fig 4) In each instance this occurred in the in tial four weeks and remained unchanged thereafter In no patient was this decrease n atrial sound—first heart sound interval due to a reduction in the P R interval on the electrocardiogram. The ventricular gallop disappeared during hospitalization in 8 patients with acute infarction who were treated with digitalis, but persisted in 5 patients despite digitalis therapy (Fig 4)

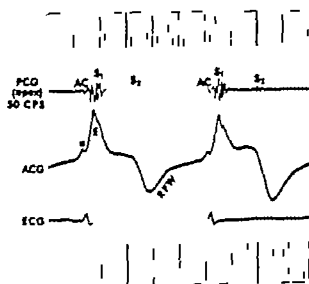


Fig 2 Similar recording on a 56-year-old man during the fourth week of hospitalization for an acute myocardial infarction. *AC* Atrial component of the first sound which is coincident with the presystolic "a" wave of the apexcardiogram

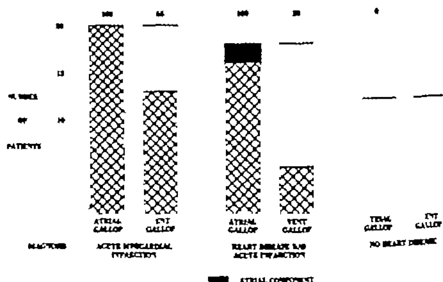


Fig. 3 A comparison of the incidence of atrial and ventricular gallops in three groups of patients admitted to the coronary care unit with chest pain

The second group (Table 1) includes 18 patients, in whom an acute infarction could not be documented but with coronary atherosclerotic and/or hypertensive heart disease diagnosed on the basis of history physical examination electrocardiograms and cardiac x ray series. Sixteen of these patients had an atrial gallop and 2 had an atrial component on admission phonocardiogram (Fig 3) Five patients had a ventricular gallop during the period of hospitalization which varied from three days to eight weeks. The atrial gallops became atrial components in 2 patients and in one ventricular gallop disappeared.

The third group (Table 1) consists of 17 patients with no evidence of heart disease by clinical examination multiple electrocardiograms, cardiac x-ray series, and serum determinations of total lipids, triglycerides, cholesterol and uric acid. Fasting and two hour postprandial blood sugars were normal in each patient. Electrocardiograms were obtained in 5 of these patients during tread

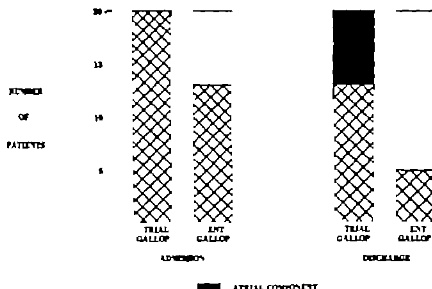


Fig 4 A comparison of the incidence of trial and entricular gallops in 20 patients with acute myocardial infarction on admission and following four weeks of hospitalization (see text)

Table I. Classification of the 50 patients followed with serial phonocardiograms

Diagnosis	N of patients	Average age (yr)
Acute myocardial infarction	20	57
Heart disease without acute infarction	18	53
Coronary atherosclerotic heart disease with previous infarction	11	
Coronary therosclerotic heart disease without previous infarction	3	
Hypertensive heart disease	1	
Hypertensive and coronary atherosclerotic heart disease	3	
No heart disease	12	46

mill exercise and showed no evidence of myocardial ischemia. None of these 12 patients had either an atrial or ventricular gallop by serial auscultation and phonocardiograms (Fig 3)

Eighty-five of the add tional 87 patients with acute infarction and sinus rhythm who were followed by serial auscultation and at least one phonocardiogram during hospitalization had documented atrial gallops. Forty-eight of these patients had ventricular gallops on phonocardiogram (Fig 5) One of the two patients with acute myocardial infarction who did not have an atrial gallop had mitral stenosis. The other patient had extensive posterior wall myocardial fibrosis extending into the left atrial wall on postmortem examination.

Discussion

A low frequency sound occurring in late diastole was first described by Charcelay in 1838.[21] This fourth heart sound auricular sound or atrial gallop originates in the ven tricle and coincides with the presystolic wave of the entricular pressure curve.[1,2,22] The audible atrial gallop occurs with the "a wave of the apexcardiogram. This dif ferentiates it from the earlier usually in audible, low frequency sound produced in the atrium. The atrial gallop has been attributed to both transient reclosure of the atrioventricular valve[1,23] and to ven tricular wall vibrations.[12,24] This presystolic sound has frequently been noted to increase in ampl tude and to occur earlier as a result of an increase in ventricular filling a prolongation of atrioventricular conduction or a decrease in left ventricular compliance.[22,11,3] An atrial gallop is fre quently but not always associated with an ncrease in ventricular end-diastolic pressure.[4,22] The administration of digitalis to patients in congestive heart failure does not

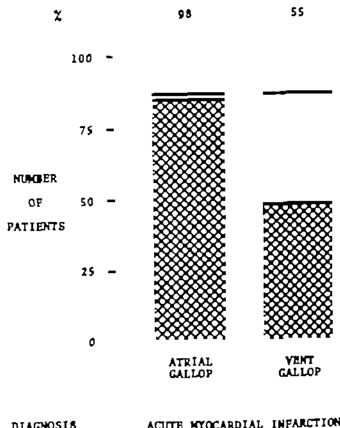


Fig 5 The incidence of atrial and ventricular gallops in an additional 87 patients with acute myocardial infarction which were followed with serial auscultation and at least one phonocardiogram.

abolish the atrial gallop or significantly alter the gallop–first sound interval.[23]

The incidence of gallop rhythm with phonocardiographic documentation in patients with acute myocardial infarction has been the subject of two previous studies. In 1942 Master and Friedman reported an 83 per cent incidence of auricular sounds in 78 patients with acute infarction. In 33 per cent (29/87) of these patients the auricular sound was of high amplitude and high enough frequency (greater than 4 cycles per second) to be termed pathologic by the authors. The low frequency atrial sounds in the other 39 patients were considered a normal variant. Ventricular gallops were demonstrated in 47 per cent of these patients.

More recently Stock[24] reported fourth heart sounds in 18 and ventricular gallops in 16 of a group of 37 patients with acute myocardial infarction. These findings were based on either auscultation or phonocardiography.

In the present study all of the 20 patients with acute myocardial infarction followed with serial phonocardiograms had atrial gallops and 85 of 87 patients with acute infarction followed with serial auscultation and at least one phonocardiogram demonstrated this finding. The combined incidence of atrial gallops in these two groups is 98 per cent (105/107).

The high incidence of recorded atrial gallops in this study confirms the clinical observations of others[9] and may be due to: (1) positioning the patient on his left side which brings the left ventricular apex closer to the chest wall (this frequently increases the intensity of atrial and ventricular gallops); (2) recording the simultaneous apex cardiogram which is helpful in localizing the left ventricular apex (this is often the only point over which the atrial gallop is heard); (3) the use of more modern equipment including a crystal microphone with a linear response from 50 to 1,000 cycles per second and a recording device that per

mitted attenuation of frequencies below 50 or 100 cycles per second. The observation of the parameters to be recorded on an oscilloscope was also of value in recording atrial and ventricular gallops. All the recorded gallops were audible and most were visible and palpable as well, corresponding to the presystolic and rapid filling waves of the apexcardiogram.

In this series the 2 patients who did not have an atrial gallop with acute myocardial infarction illustrate that acute infarction may occur without this physical finding. The first patient with mitral stenosis had obstruction to left ventricular filling and the second patient had left atrial fibrosis with presumably diminished force of left atrial contraction. An increase in atrial contraction following the administration of an inotropic agent to a patient with left ventricular decompensation may actually result in the appearance of an audible atrial gallop. This sequence of events has recently been reported in a patient with primary myocardial disease who was given intravenous ouabain at the time of left heart catheterization and while an external phonocardiogram was being recorded.[16] The authors have recently observed a patient with coronary artery disease and a myocardial infarction in the past who has an atrial gallop only when receiving digitalis. No atrial gallop could be recorded prior to or following cessation of digitalis.

A reduced contribution of atrial contraction to ventricular diastolic filling also may persist for several days following the reversion of atrial fibrillation to sinus rhythm.[17-21] In patients with coronary atherosclerotic heart disease, an atrial gallop often appears with the improvement in atrial contraction and cardiac output that occurs two to five days after reversion to sinus rhythm.[29] For this reason, the absence of an atrial gallop might be anticipated in a patient with a recent myocardial infarction for several days following reversion to sinus rhythm.

Serial phonocardiograms in 20 patients with acute infarction frequently showed the atrial gallop to move toward the first heart sound during the four weeks of hospitalization. In 7 patients it became an atrial component as defined by Kincaid-Smith and Barlow, who previously observed this decrease in gallop–first sound interval in hypertensive patients during treatment and in patients recovering from acute infarction. These atrial components were audible but, on auscultation, were difficult to distinguish from splitting of the first sound. Again correlation with the a wave of the apexcardiogram was helpful for verification. In several patients not in this study who have coronary atherosclerotic heart disease and have had a myocardial infarction in the past, it has been possible to demonstrate an atrial gallop or atrial component on phonocardiogram only at the time of mild supine exercise. In other patients an atrial component became an atrial gallop on exercise.

The 65 per cent incidence of ventricular gallops in the patients with acute infarction who had a phonocardiogram on admission is somewhat higher than in previous studies. Over 60 per cent of these ventricular gallops disappeared during hospitalization, many during the first week of recovery. A persistent ventricular gallop despite treatment for congestive heart failure is regarded by many to be of grave prognostic significance following a myocardial infarction as opposed to a persistent atrial gallop which has little prognostic value.[11,21,26] The present study would support these clinical observations to the extent that an atrial gallop or atrial component remained present throughout the period of follow-up in all 20 patients with acute infarction, all of whom survived.

The presence of an atrial gallop on admission to the coronary care unit did not distinguish patients with acute myocardial infarction from patients with heart disease who did not have an infarction. However, the presence of both atrial and ventricular gallops was more common in patients with acute infarction. None of the patients presenting with chest pain but without clinical evidence of heart disease had either atrial or ventricular gallop on auscultation or phonocardiogram. However, the authors have seen an occasional patient with an atrial gallop on auscultation who did not have other clinical evidence of heart disease.

We conclude from the present study that almost all patients with acute myocardial infarction have an atrial diastolic gallop and that the absence of this sound in a patient with chest pain and in sinus rhythm

makes the diagnosis of acute infarction less likely In addition the presence of an atrial gallop does not help to identify cardiac patients with and without infarction but it may distinguish these two groups from noncardiac patients in a similar age group who present with chest pain

Summary

Fifty consecutive patients admitted to a coronary care unit with chest pain were followed with serial phonocardiograms. Simultaneous apical phonocardiogram apex cardiogram and electrocardiogram were recorded on each patient daily in the unit and weekly during the remaining hospitalization.

All 20 patients with documented acute myocardial infarction had atrial gallops on admission Thirteen had ventricular gallops as well Seven atrial gallops became atrial components and eight ventricular gallops disappeared during hospitalization None of 12 patients without evidence of heart disease had either atrial or ventricular gallop Sixteen of 18 patients with arteriosclerotic heart disease but no acute infarction had atrial gallops and 2 had atrial components.

Eighty-five of an additional 87 patients with acute infarction had atrial gallops documented by auscultation and phonocardiogram. The exceptions were a patient with pre-existing mitral stenosis and a patient with left atrial fibrosis on post mortem examination.

The absence of an atrial gallop in a patient presenting with chest pain and in sinus rhythm makes the diagnosis of myocardial infarction less likely

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Dystrophic calcification of myocardium as conditioning factor in genesis of congestive heart failure

An experimental study

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Focal myocardial lesions are consistently present in an inbred strain of Syrian hamsters (BIO 14.6 pedigreed line) suffering from a hereditary primary myopathy that is transmitted by an autosomal recessive gene. The earliest histologically detectable abnormality in the heart muscle consisting of myolysis and/or necrosis of muscle fibers occurs around the thirtieth day of age in females and about 10 days later in males of this cardiomyopathic strain. Around the sixtieth day of age, the heart muscle degeneration already widespread involves the free walls of both ventricles and the intraventricular septum. Nevertheless, this type of spontaneous myocardial pathology is progressive until only about the eightieth day of age at which time the severity of heart muscle damage is relatively uniform in all animals of both sexes healing processes and such compensatory phenomena as hypertrophy and dilatation then begin to take place in the affected hearts.

Although it appears that in young cardiomyopathic hamsters the normal function of the heart is handicapped already prior to the appearance of focal lesions,[1] the onset and rapid progression of myocardial degeneration is an important eliciting or contributory factor in the genesis of heart failure which is also regularly observed during the advanced stages of the hereditary disease. Nevertheless, the evolution of generalized venous congestion shows a considerable biologic variation from animal to animal some obviously edematous hamsters die prior to their one hundredth day of age while others do not reach the terminal stage of congestive heart failure for another 200 to 300 days.[1] This new disease model proved to be especially suitable to analyze various aspects of the healing of focal lesions and to establish the relationship between cardiac pathology and the development of heart failure. Studies performed along these lines suggested that the speed of healing of the spontaneous, focal myocardial lesions is of more immediate importance than the extent of the original damage with respect to the occurrence of sustained cardiac decompensation.[1-7] During these investigations we noted varying degrees of calcification within the degener-

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ating myocardial areas in some cardiomyopathic hamsters but not in others. It was thought that this secondary mineralization which interferes with normal healing may be one of the reasons for the biologic variation mentioned above.

This communication describes experiments showing that whenever dystrophic calcification of the myocardium is enhanced the subsequent development of congestive heart failure becomes significantly accelerated while the prevention of calcification exerts an opposite effect.

Materials and methods

Histopathologic studies A total of 456 male hamsters of the BIO 14 6 cardiomyopathic strain were used Each group consisted of 10 animals in the first 20 animals in the second and 6 animals in the additional two experimental series the average initial age was 41 days (range 36 to 47 days) The animals were kept under identical, controlled housing conditions in air conditioned rooms with a 12 hour day night cycle. Guilford hamster chow and tap water were offered *ad libitum* except during maintenance on synthetic diets (i e low Ca and low P) when distilled water was substituted for tap water

The low-Ca diet ("Calcium-deficient diet") consisted of whole dried egg (ether extracted) 27 per cent sucrose 10 per cent lard 10 per cent dried yeast, 7 per cent cod liver oil 2 per cent starch 40 per cent. This diet also contained 4 per cent of a salt mixture that was comprised of (in grams per 100 lb.) ferric citrate, 29 462 Mg chloride 855 122 Mn sulfate, 0 414 K alum 0 190 K chloride 355 491 K citrate, 371 976 K iodide 0 085 K sulfate 37 620 Na chloride, 164.430 and Na fluoride, 1 048 The low P diet ("Phosphorus-deficient diet") was composed of purified beef blood fibrin 20 per cent cane sugar 56 per cent vegetable oil (hydrogenated) 18 per cent cod liver oil, 2 per cent. The low P diet also contained 4 per cent of the following salt mixture (in grams per 100 lb) Na chloride, 454 K chloride 682 Mg sulfate 136.2 ferric citrate 45 4 Ca carbonate, 454 Cu sulfate 5 902 Mn sulfate monohydrate, 2 034 Zn carbonate 0 705 Co chloride, 0.408 K iodide 0.364 and cane sugar 444.556 Both of these synthetic diets (prepared by General Bio-

Table I Effects of various treatments on serum and tissue calcium levels as well as the relationship between myocardial calcium concentration and severity of histochemically demonstrable mineral deposits

Group	Strain	Treatment†	Calcium: Serum‡ (mg %)	Calcium: Myocardium‡ (mg./100 Gm. dry weight)	Myocardial calcification: Severity‡§ (Grade 0-3)	Myocardial calcification: Incidence (%)
1	Healthy control (LSH)	None	9.5 ± 0.31	12.4 ± 0.28	0	0
2	Cardiomyopathic (BIO 14 6)	None	11.3 ± 0.42	108.5 ± 17.7	1.1 ± 0.17	80
3	Cardiomyopathic	$CaCl_2$ + Na_2HPO_4	12.4 ± 0.37	476.4 ± 38.9	2.3 ± 0.26	100
4	Cardiomyopathic	Low-Ca diet	8.7 ± 0.18	15.0 ± 0.31	0	0
5	Cardiomyopathic	Parathyroid powder	11.9 ± 0.46	99.4 ± 26.5	1.4 ± 0.11	90
6	Cardiomyopathic	Parathyroidectomy + parathyroid powder	10.8 ± 0.57	87.8 ± 21.7	1.2 ± 0.16	80

*Each group consisted of [illegible] animals.
†In Groups 3, 5, and 6 the last treatment was given [illegible] hours before being put to death.
‡Mean ± standard error
§Grading on arbitrary scale of sections stained with the von Kóssa $AgNO_3$ technique for further explanation, see text.

chemicals Chagrin Falls, Ohio) were supplemented with the following vitamin mixture (in grams per 100 lb) biotin 0 014 Na pantheothenate 1 134 p-aminobenzoic acid 0.245 i inositol 9 08 choline chloride 26 456 folic acid 0 1132 menadione 0.2268 nicotinic acid 3 1748 pyridoxine HCl 3 1652 riboflavin 0 272 thiamine HCl 0.272 vitamin B_{12} 0 002 alpha tocopherol 0 92 vitamin A concentrate (200 000 U per gram) 9 08 and vitamin D concentrate (400 000 U per gram) 0 92 Whenever indicated in the figures, 0 5 mM of CaCl (Fisher) per 100 Gm of body weight and/or 0 5 mM of Na_2HPO_4 (Fisher) per 100 Gm of body weight were administered in 2 ml. of water twice daily by stomach tube the controls receiving the same volume of water alone. Parathyroidectomies were performed under ether anesthesia on the first day of the experiment with the aid of thermocautery Lyophilized pork parathyroid powder (Nutritional Biochemicals Cleveland Ohio) was injected subcutaneously once daily at the dose of 0 1 Gm per 100 Gm body weight in 0.2 ml physiologic saline this level of administration maintained a normal serum calcium concentration in parathyroidectomized hamsters (Table I)

After death whether spontaneous or by sacrifice each animal was autopsied the gross pathologic findings were recorded organs were weighed and specimens were taken for routine histology These always included the heart liver and a hind leg muscle (anterior tibialis) Following fixation with 80 per cent ethyl alcohol the sections were stained with the von Kóssa $AgNO_3$ technique for the histochemical demonstration of calcium deposit with the use of a fuchsin-aniline blue counterstain

The development and healing of myocardial degeneration was analyzed by establishing the relationship between the severities of fresh or newly formed lesions and those showing varying degrees of healing An area of degeneration involving about 20 cross-sectioned adjacent muscle fibers was considered as one 'lesion unit. Three sections were prepared from each heart at different levels and the average of the total number of lesion units was taken to indicate in each case, the severity of fresh and of healing or healed degeneration The frequency i.e. average number of lesions per section of fresh and healed foci of degeneration was also established in the same sections without taking into account the variations in size of focal pathology The data so obtained were then supplemented by observations on the qualitative aspects of the healing processes. The severity of dystrophic calcification was assessed on an arbitrary scale of 0 to 3 0 no calcification 1 just detectable calcification 2 moderate calcification 3 severe calcification. To estimate the severity of congestive heart failure the degree of generalized edema histopathologic changes of the liver and congestive alterations in the lungs and other organs were evaluated A scale of 0 to 4 for the severity of heart failure, established by previous studies on the progression of various peripheral manifestations of this type of chronic congestive cardiac failure was used in the present investigations. 0, no heart failure 1 mild heart failure 2 and 3, various degrees of moderate failure 4 severe heart failure.

Electrolyte studies One additional experimental series was performed in order to establish the relationship between the myocardial calcium concentration and the grading of calcific deposits, i.e., the intensity of mineralization demonstrable by the von Kóssa technique. The same experiments served to determine the potency of the parathyroid preparation used in the present studies. Each experimental group consisted of 10 male hamsters of the BIO 14 6 cardiomyopathic strain. A group of 10 male hamsters of an unrelated healthy strain (LSH or London School of Hygiene) served as controls. The average initial age of these animals, as well as the mode of administration the daily dose, and the duration of the various treatments used were identical with those of the first experimental series

Serum and myocardial calcium were measured by an atomic absorption spectrophotometer (Perkin Elmer Model 290), as described in details earlier[8] Blood samples were obtained from the jugular vein. For myocardial calcium determinations, the lower two thirds of both ventricles were used they were dried until constant weight in a silica-gel desiccator at 1 mm. Hg and then ashed with a 1 2 mixture of concentrated perchloric and nitric acids at 100

to 120° C Teflon beakers were used for all steps of processing and measuring the samples. The remaining upper one third of ventricular musculature was taken for routine histochemical grading of the severity of myocardial calcification following staining with the von Kóssa technique. The results of both the calcium measurements and the histochemical observations are summarized in Table I

Results

In the first experimental series (Fig 1) the effects of various factors known to influence soft tissue calcification upon the development and healing of the spontaneous myocardial lesions were studied. The animals of Group 1 served as absolute controls and were killed on the day the experiment was started The hamsters of Group 2 also served as controls and were killed together with the survivors in the remaining 10 groups on the fortieth day of the experiment. All dietary measures and other treatments were initiated on the first day and continued throughout the observation period

Since the total number and average severity of myocardial lesions seen in Groups 2 to 12 varied only slightly and insignificantly from group to group it was reasonable to assume that none of the dietary measures and treatments used exerted any significant influence upon the underlying disease itself i.e., on the onset and progression of heart muscle pathology However as the data summarized in Fig 1 show there was an inverse relationship between the severity of calcification of the degenerating myocardial areas and the progression of healing of heart-muscle damage. Whenever the deposition of minerals was enhanced the percentage of healing and healed lesions sharply decreased (compare

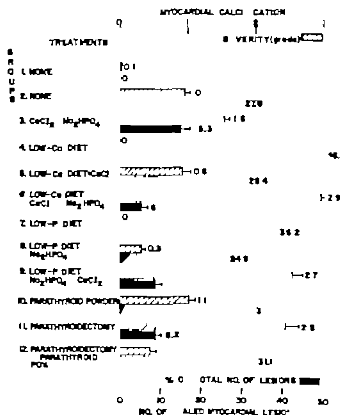


Fig. 1 Correlation between severity of calcification of degenerating myocardial areas and healing of heart muscle lesions in cardiomyopathic strain of hamsters.
Animals in Group 1 were killed on the day the experiment was started.

Groups 3 6 9 and 11 with control Group 2) but when calcification was prevented a larger number of lesions already showing evidence of early or more advanced connective tissue replacement were observed (see Groups 4 and 7)

Histochemically demonstrable calcium deposition was not *usually* present in lesions during their earliest stage of development when it did occur it was seen only in deteriorated areas. Independently of the morphologic characteristics and extent of the individual focal lesions as well as of the intensity of mineralization calcification presented itself in two different forms either deposited in degenerating muscle fibers only or involving the surrounding connective tissues also (Figs. 2 and 3) Extravasated blood appeared to be one of the factors that predisposed the parenchymal cells for calcification In such diffusely calcified degenerating areas, the viable fibroblasts and other preserved interstitial cells normally present between the deteriorating muscle fibers were absent. When connective tissue proliferation occurred in such foci it was seen only at the periphery of the lesion. Thus, the influence of calcification upon the progression of healing of myocardial pathology was obvious both from a quantitative and qualitative point of view It is noted that the skeletal muscle lesions, also consistently present in these hamsters, showed less tendency to calcify than the heart muscle lesions. Nevertheless, in general, the variations in the onset and severity of calcification followed the same direction in all striated muscles. It is noted in this connection that the von Kóssa $AgNO_3$ technique should not be considered as a histochemical method specific for calcium[8] and hence, the use of the term mineralization instead of calcification appears to be more appro-



Fig 2 Dystrophic calcification largely restricted to degenerating myocardial fibers. Not intense connective tissue proliferation between calcified muscle fibers. Left ventricular wall of an 81-day-old cardiomyopathic hamster (See Fig 1 control Group 2) (von Kóssa and fuchsin-aniline blue × 400)



Fig 3 Diffusely and heavily calcified focal lesion showing connective tissue proliferation only at the peripheries. Right ventricular wall of 81-day-old parathyroidectomized hamster of cardiomyopathic train. (See Fig 1 Group 11) (von Kóssa and fuchsin-aniline blue; × 400.)

priate on theoretic grounds. Nevertheless, it is remarkable that, in the present studies, a satisfactory positive correlation was demonstrated between the variations of myocardial calcium concentration and the histochemical grading (see Table I). This finding supports the assumption that large portions of the mineral deposits tangible with the von Kóssa technique are calcium salts.

In the second experimental series (Fig. 4) the effects of various factors upon the development of congestive heart failure were observed. The average initial age of the cardiomyopathic hamsters at the onset of this series, as well as the daily dose of the various treatments, were identical with those described for the first series. In the majority of groups, the treatments, including feeding of synthetic diets, were again terminated after 40 days, but the long term effects of such temporary variations in electrolyte intake were followed for an additional 10 weeks. This arrangement could not be used in the parathyroidectomized animals (Groups 11 and 12) and hence, the parathyroid preparation was injected continuously to the appropriate groups (Groups 10 and 12) throughout the duration of the experiment. The hamsters of control Group 1 were killed on the fortieth day in order to establish the degree of congestive heart failure existing at the time when the majority of treatments were discontinued. The survivors of the remaining Groups 2 to 12 were killed on the Day 111.

It is evident from the data recorded in Fig. 4 that a moderate to severe congestive heart failure developed in 63 per cent of the untreated controls (Group 2). It is also clear that the same treatments that enhanced the intensity of dystrophic calcifi-

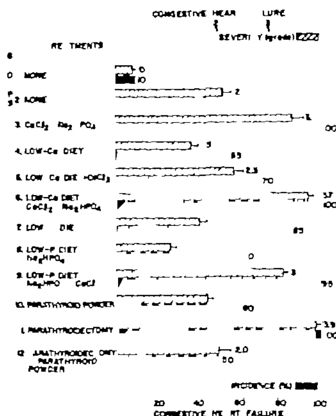


Fig. 4. Effects of various treatments (which were shown to influence myocardial calcification) upon development of congestive heart failure in cardiomyopathic strain of hamsters.

Animals in Group 1 were killed on the fortieth day of the experiment, when treatments in the majority of other groups were discontinued.



Fig 5 R lationship between myocardial calcification and subsequent development of congestive heart failure *Left* Heart enlargement (weight 598 mg) and liver congestion (weight 1,656 mg) in a animal treated with CaCl and Na HPO (see Fig 6 Group 3). *Right* Absence of obvious heart enlargement (weight 380 mg) and liver congestion (weight 812 mg) in an mal maintained on a low-Ca diet (see Fig 6 Group 4). Both cardiomyopathic hamsters were 148 days old t time of a topsy

cation in the myocardium in the first experiments accelerated the development of congestive heart failure in the present series (compare Groups 3 6 9 and 11 with Group 2) while the dietary measures that proved effective in preventing mineral deposition in the first series exerted a long term beneficial effect here (Groups 4 and 7) The protective or aggravating influence of the different treatments upon the development of congestive heart failure (Fig 5) was also well reflected by the mortality rate, which varied as follows Group 1 0 per cent 2 50 per cent 3 100 per cent 4 10 per cent 5 65 per cent 6 90 per cent 7 30 per cent 8 10 per cent 9 95 per cent 10 50 per cent 11 100 per cent 12 40 per cent The average survival time of the animals that died was 96 days in control Group 2 and 67 71 79 and 61 days in Groups 3 6 9 and 11 respectively

Scattered fibrotic areas and well-defined scars constituted the characteristic morphologic findings in hearts of animals without any significant degree of congestive heart failure, mineral deposits being only occasionally observed However in the enlarged hearts of hamsters with moderate to severe degrees of venous congestion the majority of focal lesions were filled with calcific deposits. Calcified foci evidencing phagocytosis were usually in a more advanced stage of healing than those without any significant cellular invasion In general, a comparison of the morphology of hearts with and without dystrophic calcification indicated that the onset of secondary mineralization considerably delayed the normal organization of the myocardial lesions by connective tissue. Since all the peripheral manifestations of heart failure were regularly more marked in animals with calcified myocardial lesions than in those cardiomyopathic hamsters in which such dystrophic calcification was either less intense or totally absent the working hypothesis was advanced that dystrophic calcification influences the development of congestive heart failure by affecting the normal reparative processes in the structurally severed myocardium

Two additional experiments were performed in order to gain further support for the assumption that there is a definite relationship between the severity of dystrophic calcification of the myocardium and the

onset and development of congestive heart failure. In one such study the experimental arrangements were identical with those of Groups 2 to 9 of the second series, except that the duration of treatments was extended from 40 to 63 days. Such prolonged treatments did not significantly enhance the extent of aggravation of and protection against the development of congestive heart failure. Finally in the last experiment, a short term (20 day duration) period of treatment was started at the age of weaning and terminated prior to that phase of the disease when the majority of focal myocardial lesions usually develop. The onset and progression of heart failure was not altered under these experimental conditions.

Discussion

The principal outcome of these studies is the demonstration that enhancement of calcification of the myocardial lesions that occur spontaneously in the BIO 14 6 strain of hamsters significantly accelerates the subsequent development of congestive heart failure, while the prevention of dystrophic calcification exerts an opposite effect. Since there was an inverse relationship between the severity of calcification of the degenerating heart muscle areas and the progression of healing of these lesions, it was assumed that dystrophic calcification influences the development of congestive heart failure by affecting the normal reparative processes in the structurally severed myocardium.

Since the results under discussion are equally compatible with the assumption that inhibition of healing promotes calcification of the lesions, whereas improvement of healing prevents calcification these possibilities were also considered It was observed that the speed of normal reparative processes can be influenced without exerting any significant effect upon the onset and intensity of dystrophic calcification More precisely treatment with actinomycin D markedly delayed or even completely inhibited healing while the administration of anabolic hormones (growth hormone, testosterone, and insulin) accelerated the reparative processes. The secondary mineralization of the lesions was not affected by these treatments. However the experiments just mentioned clearly revealed that an inhibition of healing no matter how induced (i.e., by enhancement of dystrophic calcification or by inhibiting connective tissue proliferation with actinomycin D) is followed as a rule by an acceleration of the subsequent development of congestive heart failure.

It has long been postulated that dystrophic calcification may impair the healing processes in injured hearts.[10] Detailed information is lacking however concerning the relationship between calcification of cardiac lesions and the subsequent occurrence of heart failure. This is mainly because in most of the earlier pertinent studies either the severity of dystrophic calcification could not be influenced selectively without affecting the accompanying tissue damage [11-13] or when such dissociation was successfully accomplished [13,14] the experimental disease model did not result in heart failure

Therefore it is important to stress that in the present studies, variations in calcium and phosphorus intake as well as parathyroidectomy influenced merely the severity of calcification of the deteriorating myocardial areas, but not the occurrence and progression of the cardiac muscle degeneration Thus, the hereditary cardiomyopathy of the hamster provides a new possibility for future studies on the mechanism of dystrophic calcification and on potential therapeutic measures.

Finally it is stressed that the presence of dystrophic calcification is not a prerequisite for the subsequent development of congestive heart failure in the cardiomyopathic hamsters, but merely acts as a conditioning factor by accelerating the progression of generalized venous congestion Since, depending upon as yet unclarified conditions, dystrophic calcification may or may not occur in hearts of untreated cardiomyopathic hamsters, its presence or absence obviously contributes to the great biologic variability normally seen at the time of onset and during progression of congestive heart failure in the BIO 14 6 inbred line.

Summary

Focal myocardial lesions are consistently present in an inbred strain of Syrian ham-

sters (BIO 14 6 line) suffering from a hereditary primary polymyopathy The onset and rapid progression of myocardial degeneration play an eliciting or contributory role in the genesis of congestive heart failure which is also regularly observed during the advanced stages of this hereditary disease. Under the present experimental conditions, variations in calcium and inorganic phosphorus intake, as well as parathyroidectomy influenced the secondary calcification of the myocardial lesions but not the extent of focal degeneration itself Enhancement of dystrophic calcification accelerated the subsequent development of congestive heart failure while the prevention of calcific deposits afforded a protective effect. Since an inverse relationship was established between the severity of calcification of the degenerating heart muscle areas and the progression of healing of these lesions it is postulated that dystrophic calcification influences the development of congestive heart failure by affecting the normal reparative processes in the damaged myocardium In fact it was shown that dystrophic calcification interferes with healing not only mechanically but also qualitatively it alters the normal healing patterns. Calcification appears to be an important conditioning factor in the genesis of heart failure in the hamster

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Muscle blood flow in normal and hypertensive subjects

Influence of age exercise and body position

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At rest, uncomplicated and established essential hypertension is hemodynamically characterized by a normal cardiac output and increased total peripheral resistance. This increased resistance is shared in a different grade by several vascular beds the vascular resistance is relatively more increased in the kidneys, [-4] and probably also in the splanchnic bed and in the skin.[4-7] Cerebral circulation[8,] shares the increased resistance in an almost equal way as the total vascular bed while measurements of the total forearm flow (skin and predominantly muscle flow) indicate that the vascular resistance in this part of the body is increased but proportionally less than in the total circulation. [11]

During exercise in hypertensive patients the total peripheral resistance decreases [12,13] but at all levels of exercise it is found to be greater in hypertensive than in normal subjects.[14]

The xenon clearance technique enables a quantitative determination of local muscle blood flow (excluding the skin) The purpose of the paper is to compare this flow in hypertensive and age matched normal groups both at rest and after maximum ischemic exercise in different body positions the results obtained for this particular vascular bed will be compared to the data published previously for the total circulation.[14]

Technique and procedure

The blood flow in the tibialis anterior muscle was measured after injection of 50 μc ^{133}Xe in this muscle as described by Lassen and associates.[15] The ^{133}Xe disappearance curve was first registered at rest recumbent and then at the moment of maximum flow after exhaustive leg exercise (rhythmic extreme flexion and extension in the ankle joints 40 times a minute, while large pneumatic cuffs are applied around the thighs inflated to above systolic blood pressure) †

The blood pressure was measured with a

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cuff around the upper arm using phase 4 of the Korotkoff sounds for the diastolic blood pressure both at rest and at the moment of maximum blood flow The mean blood pressure (BP) was calculated as the sum of the diastolic and one third of the pulse pressure. The resistance was expressed in conventional units and calculated using the following formula

$$Resistance = \frac{mean\ BP\ (in\ mm\ Hg)}{flow\ (in\ ml\ /min./100\ Gm\ tissue)}$$

In some subjects the blood flow after exhaustive ischemic exercise was also determined in the sitting and standing position

Selection of subjects

The hypertensive patients, only males, had a recumbent blood pressure of 140/90 mm Hg or more on repeated determinations, the severity of the disease varying between mild and malignant hypertension. None were in heart failure and none had clinical evidence of occlusive vascular disease in the legs. All patients were without treatment for one month Forty-one patients were included in this study 37 had essential hypertension 2 renovascular hypertension and 2 chronic glomerulonephritis. The mean blood pressure averaged 139 1 mm Hg

The 24 normal subjects were male volunteers recruited from both the hospital personnel and the hospitalized subjects without evidence of organic disease. In particular they all were normotensive had a normal heart and peripheral circulation on physical examination and history a normal ECG a normal chest x ray and no respiratory diseases. Their mean blood pressure averaged 89.2 mm Hg

Both hypertensive and normal subjects were divided into 3 groups according to their age Group I included subjects 17 to 34 years of age Group II those subjects 35 to 49 years of age and Group III subjects 50 to 75 years of age

Results

The number of determinations corresponds to the number of legs examined.

1 *Influence of age upon muscle blood flow and resistance at rest into recumbent position* Table I gives the mean and standard deviation for 48 experiments in normal subjects (18 in Group I 14 in Group II, and 16 in Group III) and 82 determinations in hypertensive subjects (24 in Group I, 30 in Group II and 28 in Group III). With age there was a slight decrease in the muscle blood flow at rest and a slight increase in resistance which was not significant ($p > 0\ 1$) Both muscle blood flow and resistance were significantly higher in the hypertensive than in the normotensive group ($p < 0\ 01$) There was a positive correlation between the blood flow (y) and the mean blood pressure (x) for the youngest group of subjects, both normal and hypertensive, the correlation ($r = 0\ 59$) was significant ($p < 0\ 001$) and corresponds to the following regression line.

$$y = 1\ 70 + 0\ 017\ x.$$

2 *Influence of ischemic exercise on muscle*

Table I *Muscle blood flow and resistance at rest recumbent in hypertensive and normal subjects*

Age group	Blood flow at rest (mL/min./100 Gm. tissue)		Vascular resistance at rest (units)	
	Normal $\bar{x} \pm s.$	Hypertensive $\bar{x} \pm$	Normal $\bar{x} \pm s.$	Hypertensive $\bar{x} \pm s$
I	3 36 ± 0 92	4 15* ± 0 90	27 9 ± 8 9	36 4 ± 10 0
II	3 22 ± 0 78	3 86 ± 0 75	29 4 ± 7 8	36 8* ± 10 2
III	3 15 ± 0 55	3 82 ± 0 94	29 5 ± 5 4	38 1† ± 9 3

*P value < 0.01 when compared to normal group of same age.
†P value < 0 001 when compared to normal group of same age.

Blood flow and resistance in normal and hypertensive subjects in the recumbent position Table II gives the mean and standard deviation of the same number experiments after ischemic exercise. In the normal subjects the maximum muscle blood flow decreases with age (Fig 1) The vascular resistance in the normal population is significantly higher (0 01 > p > 0.002) in Group III compared to Group I In the hypertensive population the same trend is seen. Muscle blood flow after ischemic exercise is not significantly higher in the hypertensive than in the normal subjects of corresponding age but the vascular resistance in the muscles is significantly higher in hypertensive than in normal subjects (p < 0 001) The increase in blood flow from rest to the maxi

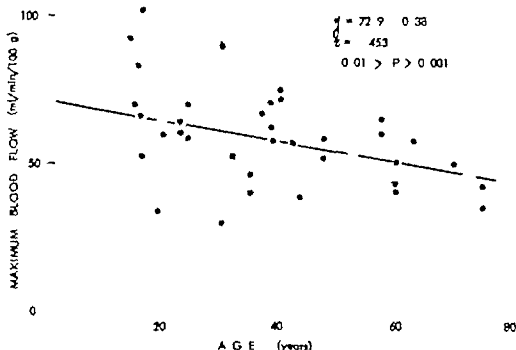


Fig 1 Maximum blood flow in normal subjects of different ages.

Table II Muscle blood flow and resistance after maximum ischemic exercise recumbent in normal and hypertensive subjects

Age group	*Blood flow after exercise (ml /min./100 Gm. tissue)*		*Resistance after exercise (units)*	
	Normal m ± s.	*Hypertensive* ± s.	*Normal* ± s.	*Hypertensive* x̄ ±
I	64 1 ± 19 6	69 2 ± 26 6	1 49 ± 0 51	2 38† ± 0 93
II	57 2 ± 13 1	58 5 ± 13 6	1 67 ± 0 53	2 46† ± 0 7
III	49 3 ± 9 3	55 6 ± 20 8	1 88 ± 0 30	2 72† ± 0 7
Total	57 2 ± 15 9	60 5 ± 21 1	1 67 ± 0 47	2 51† ± 0 8

P value > 0 1 when compared to the normal group of the same age.
†P value < 0 001 when compared to the normal group of the same age.

Table III Muscle blood flow after maximum ischemic exercise in three body positions in normal and hypertensive subjects

Body posture	Blood flow after exercise (ml./min. 100 Gm. tissue)	
	Normal $\bar{x} \pm s$	Hypertensive $\bar{x} \pm s$
Recumbent	60.9 ± 18.0	65.4 ± 29.1
Sitting	56.7 ± 15.5	54.1 ± 18.1
Standing	50.3 ± 18.1	43.7* ± 13.3

*P < 0.001 when compared with the recumbent position in same population using the method of paired comparison

mum level after ischemic exercise is about 17 times in the normal and about 15 times in the hypertensive population

3 *Influence of body posture upon the muscle blood flow and resistance measured after ischemic exercise in normal and hypertensive subjects* In 38 experiments (20 in normal and 18 in hypertensive subjects) the blood flow was determined after maximum ischemic exercise in three body positions recumbent sitting and standing The sequence of the three determinations was randomized The age distribution in the normal and hypertensive population was not significantly different In the hypertensive and normal population (Table III) the muscle blood flow after maximum ischemic exercise was significantly lower ($p < 0.001$) in the upright position

Discussion

Although xenon blood flow measurements give slightly lower values both in vitro compared with metered blood flow[4] and also in vivo in humans compared to blood flow determined by plethysmography[17] most authors find the method valid in the circumstances of their test system The decrease in muscle blood flow with age in normal subjects described here confirms earlier work[9]

On the other hand Larsen and associates[13] using the same technique found no statistically significant decrease of the muscle blood flow with age However their study was limited to subjects over a narrow age span Our normal Groups II and III having a blood flow after maximum ischemic exercise of 57.2 and 49.3 ml. per minute per 100 Gm respectively were also not significantly different, but by extending the age limits the differences became significant.

The decrease in muscle blood flow determined by the xenon clearance technique could be due to a real decrease in muscle blood flow or to variations, specific to the xenon clearance but not related to blood flow Indeed muscle blood flow measurements with xenon require the knowledge of a partition coefficient this factor has been determined only for normal dogs[20] where it was found to be 0.7 It varies with the hematocrit and fat content of the muscle. Since the latter increases with age,[8] it is feasible that at least part of the age-associated decrease of muscle blood flow would rather be related to a specific diminution in xenon clearance than in muscle blood flow itself[21,22] The tibial anterior muscle was therefore chosen for this study since it shows only minor changes in fat content with age

Our data obtained by the xenon clearance technique on the blood flow in the calf muscle extend the earlier work of Allwood[9] Using venous occlusion plethysmography he compared the total blood flow in the calf between young (18 to 24 years) and old (70 to 82 years) normal males and found a decrease with age both in the blood flow at rest and during reactive hyperemia which was however not statistically significant Since a tendency to decreased flow with age was also found with the plethysmographic technique, it is unlikely that the decrease measured with xenon was only due to changes in the partition coefficient.

In calculating the muscle blood flow in hypertensive subjects we used 0.7 as a uniform partition coefficient this assumption has been made also by all workers in the field No differences in blood flow and resistance were found between essential and secondary hypertension although the small numbers do not permit definite statement. Both muscle blood flow and vascular resistance at rest were abnormally high in hypertensive subjects when compared to age-matched normal groups assuming a normal cardiac output this suggests that in

hypertension the muscle blood flow shares the increased resistance but to a lesser degree than the total circulation. During the period of high flow after ischemic exercise the hypertensive subjects are able to decrease their resistance in the muscle studied here, but it remains higher than in the normal subjects.

The comparison in normal subjects between the local muscle blood flow studied in present experiments and the total circulation investigated previously[24] permits following speculations. Both local and total blood flow decrease with age this decrease was not highly significant for the rest flow but was highly significant for the maximum flow The limitation of exercise in elderly people is often attributed to decrease in cardiac output with age the data suggest that the peripheral muscle flow could also be a limiting factor At rest and at the maximum blood flow level the total and local vascular resistance shows a tendency to increase with age. Assuming the upright position the local blood flow shares the decrease in flow with the cardiac output

The comparison in hypertensive patients between blood flow in the tibial anterior muscle and the total circulation studied previously[14] permits the following speculations. The phenomena observed when comparing local and total blood flow in normals are also present here. Frohlich and associates[30] found a greater reduction in cardiac output during a 50 degree head-up tilt in hypertensive subjects than in normotensive subjects here the decrease in the local muscle blood flow after ischemic exercise when assuming the upright position was greater in the hypertensive than in the control population Thus, there are many similarities between the behavior of the peripheral vascular bed and that seen in the general circulation.

However to which extent differences between hypertensive and normal subjects described here are due to the hypertension per se or to the secondary changes of the blood vessels remains to be established

Summary

Blood flow in the tibialis anterior muscle was measured using the [133]Xe local clearance technique in hypertensive and normal male subjects of different ages, at rest, and after maximum ischemic exercise recumbent, sitting and standing Muscle blood flow measured by this technique decreases with age both in hypertensive and normal subjects.

At rest in hypertension both muscle flow and resistance are increased compared to the normal group indicating that the muscle vessels share the increased resistance, but probably to a lesser extent than the total circulation Assuming the upright position muscle blood flow determined after ischemic exercise decreases in normal subjects this change was even more pronounced in hypertensive patients.

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Effects of interaction of quinidine and beta blocking agents on some cardiodynamic and hemodynamic parameters of normal individuals

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In a series of pharmacologic and clinical papers[1-3] the interest and the importance of the association of quinidine with propranolol in the treatment of cardiac arrhythmias was pointed out.

In particular it was shown quite recently both in isolated heart and in humans, that the negative inotropic effect of the two drugs tended to decrease significantly when propranolol and quinidine were administered jointly.[4] This observation was extended also to other beta blocking agents and it was noted on the isolated rabbit heart, that the reduction of the negative inotropic effect observed after the association of the different antiarrhythmic drugs seemed more strictly related to the unspecific anesthetic-like properties of the beta-blocking agents than to their typical sympatholytic activity. This was true in regard to *d*-propranolol which was more active in reducing the negative effect of quinidine than the *dl* form and of (αS βS) butidrine which was more active than the (αR βR) isomer.

That the different beta-blocking compounds possess in addition to the specific sympatholytic activity also some aspecific quinidine-like properties is well known.

Butidrine is a new beta blocking agent, namely 2 sec. butylamine 1 (5 6 7,8-tetra hydro-? naphthyl) ethanol-HCl (Recetan Simes) synthetized by Ferrari Casagrande and Canova.[11] It closely resembles propranolol in its chemical constitution and it shows a definite beta-adrenergic blocking activity both in vivo and in vitro without apparent beta adrenergic stimulation.[12] Its general pharmacologic properties were extensively documented by many authors.[12-15]

Quite recently Ferrini[13] described some interesting pharmacologic actions of the stereoisomers in which butidrine can be resolved. In particular it was observed that the stereoisomer (αR βR) butidrine

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shows a striking beta blocking activity with no other unspecific property; conversely, the stereoisomer (αS, βS) butidrine is deprived of a marked sympatholytic action but is endowed with remarkable unspecific anesthetic-like properties.

The aim of the present investigation was to add to the data obtained on the rabbit heart with the association of quinidine and the two isomers of butidrine by employing some healthy human volunteers and by studying with bloodless methods and reliable yet simple laboratory techniques the effects of the above combination of drugs on the cardiovascular function of man.

Materials and methods

Experiments were carried out on 31 normal individuals of both sexes, ranging from 20 to 33 years of age, with an average age of 26 years. Different cardiodynamic and hemodynamic parameters were studied as follows: (1) 53 experiments in basal conditions (control values); (2) 44 experiments, 22 of which were performed after slow intravenous injection of (αR, βR) butidrine (BTI I) and the remaining 22 performed after (αS, βS) butidrine (BTI II) in the amount of 1.5 mg. per kilogram, respectively (measurements were taken 2, 5, 10, and 15 minutes after injection); (3) 21 experiments after three day therapy with quinidine sulfate (1.5 Gm. daily) (measurements were carried out two hours after the last 0.2 Gm. administration of quinidine); (4) 10 experiments after injection of BTI I and 10 after BTI II in subjects pretreated with quinidine as previously described.

By means of a Sanborn No. 564 polybeam the following parameters were calculated: (1) heart rate per minute (HR); (2) P-R interval in milliseconds (P-R); (3) electric systole time in milliseconds (EST); (4) deformation time in milliseconds (i.e., interval from beginning depolarization to the first heart sound) (Q-S$_1$); (5) mechanical systole time in milliseconds (S_1-S_2) measured from the first major vibration of S_1 to the first major vibration of the second heart sound S_2; (6) pre-ejection period or tension time in milliseconds (i.e., from the onset of the QRS complex to the beginning upstroke of the indirect carotid pulse) (TT = Q-S_1 + ICT); (7) left ventricular ejection time in milliseconds (LVET) (i.e., from the beginning upstroke to the trough of the dicrotic incisure of the indirect carotid pulse); (8) isometric contraction time in milliseconds (ICT) calculated by subtraction of LVET from mechanical systole; (9) ejection time/tension time ratio (ET/TT).

Other parameters measured indirectly were: (10) arterial pressure in millimeters of mercury measured with a common sphygmomanometer; (11) diastolic pressure (DP); (12) mean arterial pressure (MAP) in millimeters of mercury calculated according to the formula DP + 0.42 (systolic pressure − diastolic pressure); (13) cardiac output (CO).

Cardiac output was determined with a dye dilution curve with a Waters earpiece connected with a Sanborn adapter and a model 130 Sanborn computer. The dye was Coomassie blue (2.5 ml. of a 1 per cent solution intravenously). The number (N) given by the computer is linearly proportional to the area of the dilution curve; since this one in its turn is inversely proportional to cardiac output, keeping the quantity of dye constant, the ratio 1/N (number given by the computer) was taken as the index of cardiac output. Data were thus simply obtained, avoiding at the same time the sources of error connected with the transformation of the area of the curve into dye concentrations.

Therefore, results concerning cardiac output and related parameters (stroke output [SO], peripheral resistances [PR], left ventricular work [LVW]) were expressed, according to Bruce and Shillingford,[17] as per cent changes after administration of the beta blocking drug in comparison with basal levels or after quinidine pretreatment levels, respectively. The significance of the differences was tested by means of regression lines.

Statistical evaluation of cardiodynamic results was performed on the data directly obtained with the polygraphic method as regard to heart rate and deformation time. Since other parameters varied inversely with heart rate, they were corrected according to Wessler and associates[1] as we reported in previous papers.[5,18]

Every cardiodynamic, electrocardiographic, and pressure result obtained in basal conditions or after administration of

Table I. Means ± S.E. of cardiodynamic and electrocardiographic parameters and of diastolic and mean arterial pressure values after administration of the two isomers of butidrine (BTI I and BTI II), quinidine, and associated drugs

Parameters examined	*Control values*	*BTI I*	*BTI II*	*Quinidine*	*BTI I and quinidine*	*BTI II and quinidine*
HR	76.53 ± 1.54	66.19 ± 1.99	69.85 ± 2.70	77.61 ± 2.54	65.10 ± 1.63	76.70 ± 2.27
Q-S₁	59.83 ± 1.18	67.50 ± 1.88	65.00 ± 2.38	65.23 ± 2.27	66.90 ± 2.22	64.70 ± 3.58
ICT	36.00 ± 1.11	42.51 ± 2.07	41.01 ± 2.22	39.53 ± 2.13	38.27 ± 2.87	38.39 ± 1.99
LVET	283.20 ± 3.09	279.48 ± 5.14	288.05 ± 4.51	281.78 ± 4.70	288.81 ± 6.87	291.35 ± 6.33
S₁-S₂	324.33 ± 3.93	327.25 ± 6.19	331.42 ± 5.83	323.37 ± 5.28	325.99 ± 8.05	333.12 ± 6.68
ET/TT	3.01 ± 0.05	2.51 ± 0.05	2.74 ± 0.08	2.71 ± 0.08	2.76 ± 0.09	2.87 ± 0.15
P-R	167 ± 0.19	171 ± 0.36	179 ± 0.33	175 ± 0.40	198 ± 0.57	195 ± 0.58
EST	361.73 ± 4.27	357.85 ± 7.41	361.85 ± 6.92	359.47 ± 8.98	385.25 ± 10.86	397.32 ± 7.88
DP	87.25 ± 1.60	101.00 ± 3.84	94.58 ± 3.43	89.71 ± 2.88	99.10 ± 3.73	101.30 ± 2.51
MAP	105.61 ± 1.96	112.99 ± 3.94	107.54 ± 3.89	108.50 ± 2.68	114.36 ± 4.39	112.39 ± 2.40

Abbreviations: HR, Heart rate per minute; Q-S₁, deformation time in milliseconds; ICT, isometric contraction time in milliseconds; LVET, left ventricular ejection time in milliseconds; S₁-S₂, mechanical systole time in milliseconds; ET/TT, ejection time/tension time ratio; P-R, interval in milliseconds; EST, electric systole time in milliseconds; DP, diastolic pressure; MAP, mean arterial pressure.

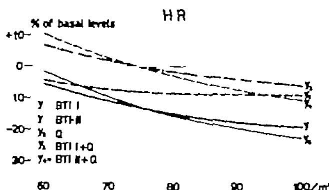


Fig. 1. Heart rate. The ordinate (y) stands for per cent changes in comparison with basal levels. The abscissa (x) stands for beats per minute. Each hyperbolic curve corresponds to the general form: $y = \frac{+ bx}{x}$

BTI I, BTI II, quinidine, and associated compounds was tested at the factorial analysis of variance to evaluate the degree of significance of the activity of the single compounds as well as of their interactions. All the calculations were performed by means of a model 101 Olivetti computer.

Results

Results obtained are referred to the comparison of the BTI I and BTI II activities and their respective interactions with quinidine.

Activities of isomers BTI I and BTI II. Data concerning cardiodynamic parameters are summarized in Table I. It appears from the tabulated results that changes observed after administration of the two isomers of butidrine are essentially of the same kind and intensity. It must be noted, however, that whereas the specific beta blocking isomer (BTI I) had a more pronounced though nonsignificant effect on diastolic and mean arterial pressure, the unspecific isomer (BTI II) was prominent on the P-R interval. On the ejection time (LVET) and on mechanical systole time the effect of both isomers was negligible.

The effects of the single or associated compounds on heart rate are explained in detail in Fig. 1, which shows that BTI I had a negative chronotropic effect proportional

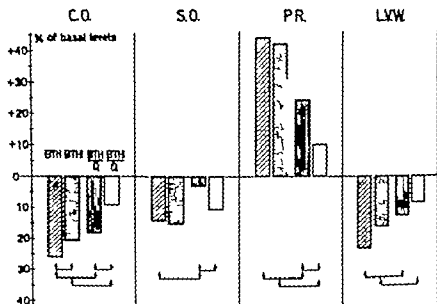


Fig 2 Per cent changes in some hemodynamic parameters (CO SO PR LVW) after BTI I and BTI II are compared with basal levels or compared with levels obtained after quinidine pretreatment. Arrows indicate significant differences calculated by means of regression lines.

to the basal heart rate Conversely BTI II had constantly the same activity

Fig 2 shows the behavior of the hemodynamic parameters not included in Table I It appears that the activity of the two isomers is not significantly different in regard to stroke output left ventricular work (LVW) and P R segment (P R) whereas BTI I shows a significant decrease in cardiac output (CO)

Activity of quinidine The action of quinidine on the examined parameters was never exceedingly striking in our experimental conditions. Apart from some significant changes of the deformation time (Q-S) and electrical systole (EST) ET/TT index and P R segment, other parameters were scarcely modified if at all

Interaction of both isomers of butidrine with quinidine It appears from the observation of Table I that values obtained after administration of the two isomers of butidrine with quinidine on many cardiodynamic parameters were inferior to those which would be the result of the sum of the single drugs administration Table II shows also the significance of the interaction of these drugs when tested at the factorial analysis of variance

The negative interaction is particularly evident with regard to deformation time (Q-S_1) isometric contraction time (ICT), and ET/TT index Conversely the negative action of the two isomers on the P-R segment seemed to increase after quinidine pretreatment and the same was noted in regard to electrical systole though only with BTI II In regard to hemodynamic parameters it appears that negative effect on cardiac output of BTI I and BTI II was significantly reduced in subjects treated with quinidine compared to the same subjects in basal conditions the same was true with stroke output and left ventricular work, results being statistically significant only for BTI I The increase in peripheral resistances was strongly reduced with both isomers after quinidine treatment.

Discussion

The effects of the beta-adrenergic blocking agents on the hemodynamic as well as on the cardiodynamic parameters are well known It seems now accepted that an unspecific non-beta blocking activity might play an important role on the antiarrhythmic and inotropic effects. The present findings seem to confirm this claim. Indeed, the hemodynamic and cardiodynamic effects were very similar after administration of the two isomers, although BTI II is almost devoid of beta blocking action Negative

Table II *Significance of activities of (αR βR) butidrine (BTI I) and (αS βS) butidrine (BTI II) and quinidine as well as significance of their interactions tested at the factorial analysis of variance*

Parameters examined*		BTI I	Quinidine	Interaction BTI I/quinidine	BTI II	Interaction BTI II/quinidine
	F	8 717	0 232	2 222	3 969	1 772
HR			0 929			
	P	< 0 01	s.	< 0 05	< 0 05	s.
	F	7 825	2 612	6 905	2 575	4 519
Q-S₁			2 141			
	P	< 0 01	< 0 05	< 0 01	< 0 05	< 0 01
	F	4 962	0 415	7 153	2 968	5 064
ICT			0 797			
	P	< 0 01	n.s.	< 0 01	< 0 05	< 0 01
	F	0 007	0 146	0 612	1 826	0 015
LVET			0 004			
	P	s.	s.	s.	s.	s.
	F	1 027	0 158	0 323	1 887	0 111
S_1-S_2			0 001			
	P	s.	s.	n.s.	n.s.	n.s.
	F	18 347	3 667	23 961	2 886	10 265
ET/TT			3 768			
	P	< 0 01	< 0 05	< 0 01	< 0 05	< 0 01
	F	4 737	12 962	8 204	22 739	2 580
P-R			14 234			
	P	< 0 01	< 0 01	< 0 01	< 0 01	< 0 05
	F	0 210	14 039	1 273	0 038	0 451
EST			7 381			
	P	s.	<0 01	s.		
	F	18 827	0 739	4 093	11 208	0 884
DP			0 928			
	P	< 0 01	n.s.	<0 01	< 0 01	n.s.
	F	4 739	0 244	0 880	1 685	0 043
MAP			0 958			
	P	< 0 01	s.	s.	n.s.	s.

*For symbols, see Table I

inotropic effects were particularly remarkable especially considering isometric contraction time and ET/TT index. As it was repeatedly stated [20-22] these parameters reflect possible changes in the intrinsic contractile state of myocardium. The BTI I isomer had a more selective action on heart rate and a more pronounced activity on diastolic and mean arterial pressure this may reflect the unmasking during beta blockade of the effects of endogenous catecholamines on the alpha receptors. The BTI II isomer in its turn was more effective in prolonging the P R segment and this was caused by the unspecific anesthetic like action. The interaction of BTI I and BTI II with quinidine gave as expected from the preceding pharmacologic results obtained on rabbit heart an additional effect lower than that which would result from the sum of the single drugs administration This was evident in the cardiodynamic parameters but not in the P R segment and on the electrical systole (only for BTI II) where the two effects seem to potentiate each other These last data do not agree with the observations reached in the isolated rabbit heart but are in full accordance with the clinical results obtained after treatment with propranolol and quini

dine.[8] Finally our results seem to confirm the experiments performed on the rabbit heart which showed that the negative interaction between antiarrhythmic drugs and beta blocking agents is not only related to the beta blockade but more probably is connected also with unspecific properties. This is suggested by the fact that the interaction with quinidine is of the same order for the two isomers.

The present experiments were performed on normal individuals and the beta blocking drugs were administered acutely instead of chronically as they are used in the treatment of cardiac arrhythmias. Nevertheless in spite of these two main intuitive limitations, our findings appear to be interesting and provocative also from a therapeutic point of view.

Summary

The effects of association of two isomers of butidrine with quinidine were studied in 31 normal individuals. A series of cardiodynamic and hemodynamic parameters were considered. In general, interaction of the beta-blocking agents with quinidine gave effects inferior to those which would result from the sum of the single drug's administration. This negative interaction was particularly evident in regard to deformation time, isometric contraction time and ET/TT index. The significance and the importance of this phenomenon, which was partly observed in pharmacologic experiments on the isolated rabbit heart, is discussed.

We are indebted to and wish to thank Professor Mario Masone for his helpful advice in the statistical evaluation of our results.

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Increase in myocardial collateral capacity following drug induced coronary vasodilatation

A preliminary report

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Björk suggests that coronary heart disease is now the greatest factor limiting human life. Despite much research aimed at preventing thrombosis and atheroma as yet this illness cannot be controlled. In contrast the collateral circulation has been neglected in the search for remedies against coronary disease.

This alternative vascular pathway consists of small arterioles connecting major coronary arteries, and although it is insignificant compared with the latter the collateral circulatory system is important for survival of acute myocardial infarction. Species with few anastomoses usually succumb at once to sudden obstruction of a major coronary artery.

In normal man and dog the myocardial collaterals are comparatively well developed but are insufficient to prevent necrosis after major vessel occlusion. Within a few days, but too late to prevent infarction, the collateral vessels enlarge progressively and ultimately may transmit large volumes of blood. Thus following coronary arterial obstruction survival depends on the presence and recovery on the growth of collateral vessels.

It has been suggested that vasodilator drugs might promote collateral growth and protect against the effects of arterial obstruction when given for some time previously. Survival after gradual coronary occlusion developing over several days is claimed to be greater in pigs treated previously with dipyridamole[3] and retrograde flow from the coronary artery beyond a ligature is increased in dogs given this substance beforehand.[4] An increase in retrograde pressure has been shown following another vasodilator, lidoflazine, in dogs with gradual coronary arterial obstructions induced by constrictors.[11] In this report we show that the collateral vascular response to acute coronary occlusion measured by radioxenon clearance is increased in the normal canine heart by preliminary treatment with dipyridamole.

Methods

The experiments were done on beagles of comparable weight and age. The animals

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were healthy with normal blood counts and transaminase levels. We were limited to a total of 10 dogs, which were subdivided into two groups of similar sex distribution one to act as controls, the other to be given dipyridamole.

Because of an earlier study in which 4 mg per kilogram once daily had no effect, we gave oral dipyridamole 4 mg per kilogram three times daily for 3 months correspond-ing to the upper dose range used in man

Blood levels of the drug were estimated to confirm absorption. The animals were delivered in pairs to our laboratory at weekly intervals 2 to 4 days before the experiments, and medication ceased on arrival. We were not told which animals had received dipyridamole until the final analysis when all the experiments and re lated measurements had been completed.

Each animal was lightly anesthetized with intravenous pentobarbitone and re-spired with a modified Starling pump at a rate calculated on body weight and con-trolled by blood gas analysis. The rate of ventilation was not changed after flow measurement began In most animals a catheter was placed under radiologic con-trol in the coronary sinus at the start of the experiment, for sampling here as well as in arterial blood. The electrocardiogram and aortic blood pressure were recorded con tinuously

Control myocardial flow was then deter mined by a method of ^{133}xenon clearance previously described [8] For this purpose the left coronary artery is cannulated with a Sones catheter via the carotid artery under fluoroscopy Solutions of radioxenon are then injected into the coronary arteries and the clearance of isotope from the myo-cardium is determined by an external scin tillation counter The exponential slope of this clearance curve is obtained simulta neously by an analogue computer and its clearance rate (k) gives an accurate meas-urement of myocardial blood flow which may be redetermined after 3 to 5 minutes.

After at least two control determinations, the anterior descending coronary artery was tied at thoracotomy beyond its large septal branch halfway between the apex and atrioventricular groove. A nylon cath eter was inserted distally into the artery tied in position and its free end was brought out of the incision when the chest wall was closed

Four measurements of collateral blood flow were then made serially over the next 2 hours, without further disturbance to the an mal using a method previously de-ta led Briefly solutions of radioxenon are injected into the infarct through the cathe-ter and their clearance is measured with the external scintillation counter The exponen tial slope of this clearance curve is obtained instantaneously by the computer and the clearance rate (k) of ts first exponential is a measure of collateral blood flow which may be redetermined after 20 to 30 m n utes (Fig 1)

When the four collateral flow measure-

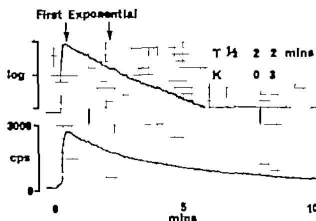


Fig 1 Illustrative radioxenon clearance from infarct in Dog D1 Original clearance slope below semilog slope from computer above, with derived *T½* and *k* measurements

ments were completed the heart was arrested with potassium removed and injected with a radiopaque solution at 100 mg Hg for 10 minutes using a standardized method for filling fine arterioles but not capillaries. The radiographs obtained were assessed independently without knowing their group for collateral vessels on an arbitrary scale.

Results

Before coronary ligation There were no significant differences between the two groups in pulse rate systemic blood pressure myocardial blood flow or arterial and coronary sinus O_2 content Details of mean systemic blood pressure (Ps) and radioxenon clearance (k) are shown in Table I

After coronary ligation One animal a control (C2) developed ventricular fibrillation but reverted to sinus rhythm with countershock and the experiment continued Following arterial ligation blood pressure was lower in the treated than in the control animals but it was not significantly lower on t test analysis ($p < 0 2$) There were no differences in pulse rate or arterial and coronary sinus O content.

Collateral blood flow was 29 per cent greater in the treated than in the control group but this just failed to achieve statistical significance ($p < 0 1$) A clearance curve from one animal (D1) is illustrated in Fig 1 Since the collateral vessels are widely dilated at this time in response to ischemia, the ratio of collateral flow to perfusion pressure (k/Ps) is a measure of collateral vascular capacity This was 56 per cent greater in treated than in control animals, a difference which is statistically highly significant ($p < 0.01$) Details of mean systolic blood pressure (Ps) collateral blood flow (k) and collateral vascular capacity are given in Table II

In 2 of the treated group and 1 of the controls the radiopaque injections were unsuccessful for technical reasons. The numbers available are thus very small but the 3 treated animals showed more collateral arterioles than any of the 4 controls.

Table I *Results of measurements before thoracotomy*

Control dogs	$\bar{Ps}$* (mm Hg)	k†	Treated dogs	$\bar{Ps}$* (mm Hg)	k†
C1	140	1 89	D1	104	1 66
	140	1 43		108	1 81
C2	146	1 01	D2	180	1 66
	132	1 07		180	1 36
C3	118	2 68	D3	140	1 30
	132	2 45		144	1 70
C4	110	1 60	D4	136	1 04
	112	2 08		138	1 01
C5	131	1 16	D5	132	1 16
	130	1 30		128	1 16
Mean	129	1 67	Mean	139	1 39

*Mean systemic blood pressure.
†Radioxenon clearance.

Discussion

For some hours after coronary arterial obstruction collateral vessels to the ischemic region are widely dilated [4,8] so that the ratio of collateral flow to blood pressure is an index of their capacity This was 50 per cent greater in those animals given dipyridamole a finding supported by the arteriographic analysis. The drug had therefore induced not only vasodilatation but also collateral vessel growth, and since it was withdrawn 2 to 4 days before the measurements the differences are not directly explained by its vasodilator effect.

The growth of collaterals in response to ischemia is well known but several days elapse before this and the resultant increase in flow develop Since cardiac muscle dies within an hour of interruption of its blood supply this growth has no immediate protective role though we have found that collaterals developed in this way around a region of myocardial scarring allowed flow rates which prevented further infarction after sudden coronary occlusion.[7]

Collateral vessel growth can also be stimulated in the hearts of animals free from coronary disease by anemia.[14] Since prolonged vasodilatation is common to both ischemia and anemia the effects of vasodilator drugs were examined. Our findings show that dipyridamole promotes collateral growth and they are in accordance with the increase in retrograde flow in dogs noted by Fam and associates[9] and the increased survival of pigs reported by Hi[illegible]

Table II Results for two hours after ligation of anterior descending coronary artery

Dog	$\overline{P}$ (*mm. Hg*)	*k*	*k*/$\overline{P}$*s*†	*Dog*	$\overline{P}$*s* (*mm. Hg*)	*k*	*k*/$\overline{P}$*s*†
C1	146	0.39	267	D1	80	0.35	438
	142	0.44	310		78	0.35	449
	136	0.36	265		80	0.33	413
	126	0.61	484		76	0.31	408
Mean	138	0.45	331	Mean	79	0.34	427
C2	96	0.07	73	D2	38	0.12	316
	86	0.12	140		56	0.18	321
	92	0.10	109		76	0.26	342
	80	0.07	88		97	0.61	629
Mean	89	0.09	102	Mean	67	0.29	402
C3	85	0.18	212	D3	112	0.18	161
	88	0.18	114		114	0.19	167
	100	0.22	220		126	0.23	183
Mean	91	0.17	179		114	0.23	193
C4	106	0.22	208	Mean	117	0.21	176
	92	0.16	174	D4	90	0.22	244
	64	0.19	297		100	0.24	240
	97	0.21	216		112	0.29	259
Mean	90	0.20	224	Mean	101	0.25	243
C5	88	0.13	148	D5	67	0.17	254
	94	0.17	181		74	0.26	351
	56	0.14	250		80	0.27	338
	60	0.14	233		80	0.25	313
Mean	75	0.15	203	Mean	75	0.24	314
Overall mean	97	0.21	208	Overall mean	88 (91%)	0.27 (129%)	313 (150%)

*Radioxenon clearance from infarct.
†Collateral vascular capacity in arbitrary units.

magyi and co-workers. It seems likely that increased vessel wall stress resulting from repeated vasodilatation is the stimulus to growth and Schaper[11] has described the cell division which permits progressive increase in the caliber of the vessel.

In man, the findings are analogous. A comparable growth of collaterals in response to ischemia has been shown repeatedly (reviewed by Fulton) and may also result from anemia in the absence of coronary arterial disease.[12] It is possible that an increase in collaterals explains the increased duration of survival noted by McNeilly and Pemberton in men dying from recurrent myocardial infarction compared with those succumbing to their first attack. Furthermore, it seems that repeated vasodilatation may promote general growth of the coronary vasculature. Currens and White[3] report an instance of prolonged physical training increasing the caliber of the main coronary arteries two- to threefold

In conclusion, there is evidence that repeated coronary vasodilatation will promote collateral vessel growth This can be achieved in animals by the vasodilator drug dipyridamole given for 3 months in a high range of dosage but one which is tolerated by man. It remains to be seen whether this growth is progressive on more prolonged administration or with more powerful vasodilator drugs. Since the de-

velopment of ischemic heart disease in man cannot be prevented these preliminary results suggest the need of clinical trials to decide whether the similar use of dipyridamole might protect those in risk of acute myocardial infarction

Summary

Dogs were given dipyridamole 4 mg per kilogram three times daily for three months and were then compared with controls following myocardial infarction caused by anterior descending artery ligation Collateral blood supply was assessed by measurement of radioxenon clearance from the infarct every half hour for 2 hours. In the treated group there was a 29 per cent increase in clearance ($p < 0.1$) and a 50 per cent increase in collateral capacity ($p < 0.01$) expressed as the ratio of clearance to perfusion pressure.

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Effects of acetazolamide on cerebral blood flow of dogs during hyperbaric oxygenation*

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Hyperbaric oxygenation produces a high concentration of oxygen in the blood and may be expected to increase the oxygen delivery to ischemic brain tissue. For this reason hyperoxia has been used in the treatment of patients with cerebrovascular insufficiency. The vasoconstrictive effect of oxygen, however, produces a decrease in cerebral blood flow and may thus reduce the availability of various substrates to the brain. Such factors may limit the possible benefits of hyperbaric oxygenation and may account for the fact that only a small proportion of patients respond to this form of therapy. The concomitant administration of cerebral vasodilating agents has been suggested in order to counteract the cerebral vasoconstriction of oxygen, to increase cerebral perfusion, and to enhance delivery of oxygen to the brain. Acetazolamide has been found to produce a significant increase in cerebral blood flow[1-4] but its usefulness in improving cerebral circulation during hyperbaric oxygenation has not been determined. The present study was designed to evaluate the effects of this agent on the cerebral blood flow of dogs during hyperbaric oxygenation and at ambient environment.

Methods

This study was carried out in 15 mongrel dogs weighing 12 to 17 Kg. The effect of acetazolamide on cerebral blood flow was determined in 7 of these 15 animals breathing room air at normal atmospheres (Group I). After duplicate base-line measurement of cerebral blood flow, each of these animals were given 5 mg. per kilogram of acetazolamide intravenously and the cerebral blood flow was determined again at 10, 30, 60, 90, and 120 minutes thereafter. In one animal the observation period was extended up to 4 hours with measurements of cerebral blood flow every 30 minutes during the last 2 hours.

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Experiments were carried out in 5 animals (Group II) to study the influence of acetazolamide on cerebral circulation during hyperbaric oxygenation. The cerebral blood flow of these animals was measured (1) while they were breathing room air at ambient pressures (2) breathing 100 per cent oxygen at 2.3 atmospheric pressure (20 PSIG) (3) breathing 100 per cent oxygen at 2.3 atmospheres and after administration of acetazolamide and (4) after they were returned to ambient pressure and were ventilated with room air. All cerebral blood flow measurements were made in duplicate except that three determinations were made after the administration of acetazolamide during hyperbaric oxygenation (at 10, 30 and 60 minutes). To determine the effect of hyperbaric oxygenation alone, the cerebral blood flow of 3 dogs (Group III) was studied in the same manner as those in the Group II but no acetazolamide was administered.

During the experiments each animal was anesthetized with chloralose and urethane (48 and 480 mg per kilogram intravenously respectively). The dogs were intubated and ventilated with a Harvard respirator through a non-rebreathing circuit. The ventilating volume was kept constant throughout the study and succinylcholine (20 mg in 250 ml of normal saline) was given in a continuous infusion to prevent spontaneous respiratory movements. The femoral artery was cannulated for monitoring aortic blood pressure and obtaining blood samples. Arterial blood pH, pO_2, and pCO were measured during each determination of cerebral blood flow. The extracranial soft tissues were surgically removed from the right side of the skull including the scalp and muscles from midline to zygomatic arch and from frontal to occipital areas. The cranium was left intact. A 21 gauge needle was inserted into the ipsilateral common carotid artery for injection of radioisotope.

The radioactive xenon clearance method as developed by Lassen and Ingvar[4] was used to measure the cerebral blood flow in these animals. A 2¼ inch scintillation probe (Nuclear–Chicago) recessed 3 cm from the end of a cylindrical collimator was placed in the center of the denuded skull of each animal perpendicular to the sagittal plane. A multichannel analyzer (Packard) with a digital read-out system was connected to the scintillation probe for the recording of the xenon disappearance curve. The pulse discriminator of the multichannel analyzer was adjusted to accept only the energy range from 70 to 110 KEV. The time of accumulation for each channel was set for six seconds. Prior to each determination of cerebral blood flow the background and residual radioactivity of the previous blood flow determinations were recorded for 5 minutes. A bolus of radioactive xenon (200 to 300 microcuries in 0.5 to 1.0 mL of normal saline) was then injected through the indwelling needle in the common carotid artery and flushed with 0.5 mL of normal saline. The disappearance curve of the radioactivity was then continuously recorded for 15 minutes after the injection.

The cerebral blood flow was calculated with the aid of a digital computer. For each xenon disappearance curve, the counts of the background and residual radioactivity recorded during the 5 minute period before the injection of xenon were first fitted to a single negative exponential by least squares. The background contribution to the disappearance curve was then calculated and subtracted from the subsequent curve. The corrected disappearance curve was then fitted by least squares to the equation $C(t) = I_1 e^{-k_1 t} + I_2 e^{-k_2 t}$ in order to solve values of k_1 and k_2. In the equation, C represents counts of radioactivity, t is the time after the beginning of the clearance of xenon, k_1 and k_2 are the slope constants of clearance for the fast flow and slow flow compartments, I_1 and I_2 are the intercepts at time zero. The blood flow of each compartment was calculated as the product of λ and k. λ is the blood tissue partition coefficient of xenon; values for λ of 0.80 and 1.50 were used for the fast and slow flow compartments, respectively.

Results

The effects of acetazolamide on cerebral blood flow in the 7 animals breathing room air at normal temperature are shown in Table I and Fig 1. The cerebral blood flow was markedly elevated 10 minutes after injection of this drug with a significant increase in mean fast flow from a base-line

Table I Effects of acetazolamide on cerebral blood flow at ambient environment (Group I)

Parameters	Control		After administration of acetazolamide				
	1	2	10 min.	30 min.	60 min.	90 min.	120 min.
Fast flow (ml./100 Gm./min.)	60.5 ± 2.8	61.1 ± 8.3	108.6 ± 31.3	112.4 ± 40.4	103.2 ± 37.1	94.3 ± 29.1	92.1 ± 29.9
Slow flow (ml./100 Gm./min.)	16.4 ± 4.1	15.9 ± 4.1	22.1 ± 6.5	24.6 ± 9.4	22.3 ± 8.0	23.1 ± 7.4	20.8 ± 8.0
Arterial pH	7.334 ± 0.033	7.382 ± 0.033	7.333 ± 0.049	7.327 ± 0.045	7.321 ± 0.045	7.324 ± 0.030	7.340 ± 0.044
Arterial pO_2 (mm. Hg)	96.7 ± 5.3	97.8 ± 9.5	97.0 ± 8.7	99.4 ± 8.6	95.6 ± 9.0	95.6 ± 10.8	95.2 ± 7.5
Arterial pCO_2 (mm. Hg)	33.8 ± 4.3	[illegible] ± 4.6	35.0 ± 4.6	34.7 ± 4.9	34.7 ± 5.4	33.3 ± 4.4	33.0 ± 3.0
Mean blood pressure (mm. Hg)	99.6 ± 10.9	101.0 ± 11.6	102.4 ± 14.4	100.0 ± 12.8	103.9 ± 11.1	101.6 ± 9.5	104.3 ± 11.0

*Mean values of 7 animals ± 1 S.D.

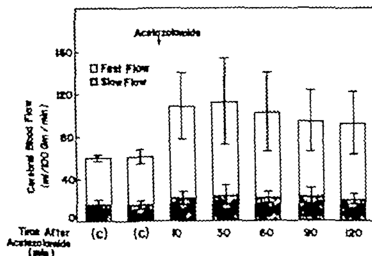


Fig. 1 Effects of acetazolamide on cerebral blood flow at ambient environment. The bar graphs represent the mean values of seven animals (open bar: fast flow; hatched bar: slow flow; vertical line, ± S.D.). Note the marked increase of cerebral blood flow after the administration of acetazolamide in comparison to controls (C).

level of 60.8 to 108.6 ml. per 100 Gm. per minute (+79 per cent) and an increase in mean slow flow from 16.. to 22.1 ml. per 100 Gm. per minute (+36 per cent). Thirty minutes after injection of acetazolamide the mean fast flow attained a peak level of 112.4 ml. per 100 Gm. per minute (+85 per cent) and the mean slow flow of 24.6 ml. per 100 Gm. per minute (+52 per cent). Although there was a gradual decrease in both fast and slow blood flow values after 30 minutes, the levels of blood flow remained greater than normal throughout the two hour observation period (see Appendix for statistical analysis). The animal studied for four hours after administration of acetazolamide showed a persistent elevation of cerebral blood flow throughout this period.

Similar changes of cerebral blood flow were observed with acetazolamide administration during hyperbaric oxygenation

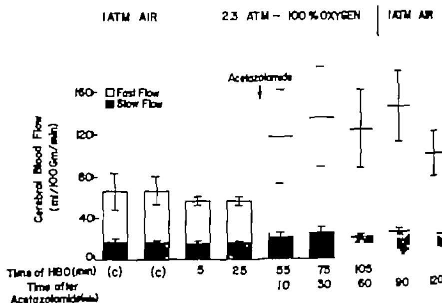


Fig 2 Effects of acetazolamide on cerebral blood flow during hyperbaric oxygenation (mean values of fi an mals) Note the increase of cerebral blood flow after the administration of acetazolamide.

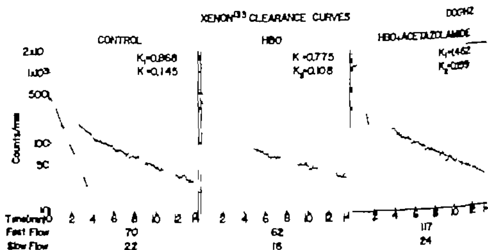


Fig 3 Examples of xenon133 clearance curves of one nimal recorded t ambient environment (*control*), during hyperbaric oxygenation (*HBO*) and after administration of acetazolamide during hyperbaric oxygenation (*HBO + acetazolamide*). The k v lues are shown t the right upper corner of each curve. The calculated values for fast flow and slow flow in mL per 100 Gm. per minute are given at the bottom of each panel

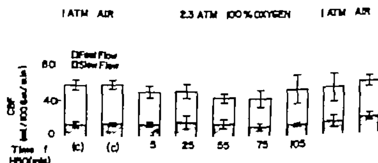


Fig 4 Changes in cerebral blood flow due to hyperbaric oxygenation. Mean values of three a imals are shown. These animals were studied in the same manner as those shown in Fig 2 except that no acetazolamide was given. Note that the cerebral blood flow did not increase a in Fig 2.

Table II Effects of acetazolamide on cerebral blood flow during hyperbaric oxygenation

Parameters	Inspiratory gas: 1 ATA† Air		2.8 ATA 100% Oxygen					1 ATA Air	
	Determination								
	1	2	3	4	5	6	7	8	9
Group II (n = 6)‡									
Fast flow (ml./100 Gm./min.)	66.4 ± 17.2	66.4 ± 13.0	65.7 ± 4.8	56.1 ± 4.3	117.8 ± 44.7	134.5 ± 47.8	133.9 ± 37.5	143.9 ± 38.6	98.3 ± 31.5
Slow flow (ml./100 Gm./min.)	17.2 ± 3.3	17.2 ± 2.0	15.0 ± 2.2	15.6 ± 1.1	20.3 ± 4.3	24.7 ± 5.2	20.0 ± 2.5	23.8 ± 3.1	20.1 ± 3.7
Arterial pH	7.360 ± 0.056	7.348 ± 0.065	7.351 ± 0.054	7.347 ± 0.073	7.315 ± 0.063	7.306 ± 0.032	7.294 ± 0.032	7.369 ± 0.033	7.375 ± 0.079
Arterial pO_2 (mm. Hg)	86.0 ± 7.1	86.2 ± 4.4	1578.0 ± 64.5	1519.0 ± 63.4	1554.4 ± 119.6	1553.2 ± 67.7	1634.0 ± 79.9	84.0 ± 13.9	83.7 ± 8.2
Arterial pCO_2 (mm. Hg)	35.3 ± 3.8	35.1 ± 4.1	37.5 ± 5.8	34.8 ± 4.2	37.7 ± 4.5	38.0 ± 2.8	37.1 ± 3.4	34.3 ± 4.1	33.0 ± 4.2
Mean blood pressure (mm. Hg)	141.0 ± 37.3	138.4 ± 30.5	127.4 ± 14.3	128.8 ± 15.3	136.0 ± 11.4	133.0 ± 14.6	137.8 ± 10.4	131.0 ± 18.4	129.0 ± 13.9
Group III (n = 6)§									
Fast flow (ml./100 Gm./min.)	60.9 ± 8.6	56.9 ± 5.4	50.0 ± 6.6	51.2 ± 7.7	43.6 ± 3.1	41.7 ± 9.2	51.3 ± 15.9	53.5 ± 15.6	46.4 ± 6.3
Slow flow (ml./100 Gm./min.)	13.9 ± 3.0	18.8 ± 1.6	14.5 ± 3.9	17.3 ± 7.8	15.0 ± 8.3	11.6 ± 2.5	13.2 ± 1.9	15.5 ± 6.4	18.7 ± 3.6
Arterial pH	7.433 ± 0.087	7.351 ± 0.036	7.334 ± 0.037	7.357 ± 0.044	7.366 ± 0.030	7.337 ± 0.046	7.310 ± 0.041	7.308 ± 0.048	7.373 ± 0.030
Arterial pO_2 (mm. Hg)	84.3 ± 5.5	80.0 ± 9.2	1461.0 ± 100.8	1473.0 ± 76.5	1508.0 ± 138.3	1530.0 ± 172.8	1474.0 ± 73.3	81.7 ± 25.4	82.3 ± 14.6
Arterial pCO_2 (mm. Hg)	34.8 ± 6.5	36.4 ± 4.5	35.6 ± 2.1	37.4 ± 5.1	37.3 ± 3.6	36.1 ± 2.0	35.0 ± 1.9	34.8 ± 1.9	35.3 ± 1.8
Mean blood pressure (mm. Hg)	134.0 ± 14.0	133.3 ± 12.9	132.7 ± 7.0	127.7 ± 12.0	135.7 ± 12.6	135.7 ± 18.6	130.3 ± 12.1	137.0 ± 15.7	153.3 ± 12.9

All values are given as mean ± 1 S.D.
†ATA, Atmosphere absolute.
‡In Group II, determinations 5 through 9 were made at 0, 30, 60, 90, and 120 min. after administration of acetazolamide.
§In Group III, all determinations were made at the same time as in Group II, but no acetazolamide was given.

(Figs. 2 and 3 Table II) When the animals were changed from breathing air at normal atmosphere to breathing 100 per cent oxygen at 2 3 atmospheres, there was an increase in mean arterial pO_2 from 86 to 1,548 mm Hg There was a concomitant reduction of the mean value of fast flow from 66 4 to 55 9 ml per 100 Gm per minute and mean slow flow from 17 2 to 15 3 ml per 100 Gm per minute. Thirty minutes after injection of acetazolamide during hyperbaric oxygenation the mean fast flow rose to a peak of 134 8 ml per 100 Gm per minute (+141 per cent) and mean slow flow to 24 7 ml per 100 Gm per minute (+61 per cent) Another small increase of cerebral blood flow was observed when the animals were returned to ambient environment.

The three dogs studied during hyperbaric oxygenation without acetazolamide (Fig 4 and Table II) showed a 12 to 8 per cent reduction of the mean values for fast flow throughout the period of hyperoxia. Immediately after returning to ambient atmosphere the mean fast blood flow value remained 8 per cent lower than the control value. During hyperbaric oxygenation the changes in the slow flow values varied from −22 to +15 per cent with a return to base-line levels after decompression

At both ambient and hyperoxic conditions, the mean arterial pCO rose slightly (1 to 3 mm Hg) in the first hour after acetazolamide injection, but thereafter the values returned to approximately the control levels. After injection of acetazolamide there was an abrupt decrease of 04 to 06 in arterial pH which remained persistently low throughout the period of observation No significant changes in mean aortic blood pressure were observed before and after the administration of this medication

Discussion

This study confirms the previous observation that an increase in arterial oxygen tension is associated with a decrease in cerebral blood flow There was a 15 per cent reduction in values for the mean fast flow and 11 per cent for the mean slow flow when the arterial pO_2 increased from 86 to 1,548 mm Hg These changes occurred without significant alterations in arterial pCO_2 or arterial blood pressure. The magnitude of the change in blood flow during hyperoxia is comparable to that found by other workers. In volunteer subjects, cerebral blood flow determined by the nitrous oxide method was found to decrease 13 per cent at 1 atmosphere of 100 per cent oxygen and 25 per cent at 3.5 atmospheres of 100 per cent oxygen[4] The animal studies by Jacobson and coworkers[8] also showed a 21 per cent decrease in the cortical blood flow at 2 atmospheres of 100 per cent oxygen (pO_2 1 100 mm Hg) as measured with radioactive krypton

Although these reductions in cerebral blood flow value are small in magnitude, they may be critical in patients in whom the cerebral circulation is already seriously compromised Of perhaps greater importance is the finding of a persistent reduction in cerebral blood flow immediately after decompression when the arterial pO_2 had returned to normal. Similar findings were observed by Jacobson and associates[8] in the animals returning to ambient environment after hyperbaric exposure As a result of the decreased cerebral blood flow the total amount of oxygen available to the brain during this period may be less than that before exposure of hyperbaric oxygenation and may be a possible factor underlying the clinical relapse of some patients immediately after decompression

The *present* study also demonstrates that acetazolamide in small amounts (5 mg per kilogram) not only effectively counteracts the vasoconstrictive effect of hyperoxia but also significantly increases cerebral blood flow during hyperbaric oxygenation. The arterial pCO_2 rose 1 to 3 mm Hg after the administration of the drug The increase in cerebral blood flow was out of proportion to the increase of arterial pCO_2, and persisted even after the arterial pCO returned to control levels. These findings agree with previous observations on the effects of acetazolamide on cerebral blood flow as measured by other methods. The total cerebral blood flow in man (nitrous oxide method) was found to increase 62 and 87 per cent after intravenous injection of 1 and 2 Gm of acetazolamide[3] In patients with cerebrovascular

insufficiency the total cerebral blood flow estimated from the cerebral A V O dif erences was found to increase 8 to 64 per cent with 500 mg and 15 to 110 per cent with 1 Gm. of acetazolamide [4,8] Eh enreich and co-workers[3] found the increase of cerebral blood flow produced by 1 Gm of acetazolamide was equal to or even more than that obtained by 5 minute inhalation of 5 per cent carbon dioxide in the same subjects.

The base line values of fast flow in this study varied from 53 to 94 ml. per 100 Gm per minute and are on the average relatively lower than those previously reported. Values for cortical blood flow in dogs as determined by krypton clearance technique were 96 and 99 ml. per 100 Gm per minute, respectively in two different studies. [14] These differences in blood flow values are probably due to the lower levels of arterial pCO_2 obtained in the present study However in our studies the arterial pCO_2 was relatively constant during each experiment and each animal served as its own control the changes in cerebral blood flow observed after administration of acetazolamide therefore, are believed to be valid The skull and meninges in our animals were not removed with the muscles and scalp and it is possible that the scintil lation probes may have detected radio isotope activity circulating in these non cerebral tissues However the circulation in these areas is slow and the mass of these tissues viewed by the scintillation probe is relatively small in comparison to that of the brain. The amount of xenon initially delivered to these areas is probably very small and the influence of the skull and meninges on our cerebral blood flow values is probably not significant

The exact mechanism by which acet azolamide increases cerebral blood flow is not clear However it has been demonstrated by Gotoh Meyer and their associates[4,8] that after administration of acet azolamide, there is an increase of tissue pCO in the brain. They suggest that acetazolamide by inhibiting the carbonic anhydrase delays the conversion of free carbon dioxide into bicarbonate in the erythrocytes and impairs carbon dioxide transport. As the result carbon dioxide accumulates in brain tissue and causes a selective increase in cerebral blood flow

It would appear that acetazolamide is an effective agent for increasing cerebral blood flow at ambient environment. Our data indicate that the drug is also effective when used in conjunction with hyperbaric oxygenation It must be emphasized however that our observations are in normal animals and may not apply to patients with cerebrovascular disease The role of acetazolamide on blood flow in the ischemic areas of the brain and its effects on the function and metabolism of the ischemic cells remain to be determined

Summary

The effect of acetazolamide in improving cerebral blood flow and counteracting hyperoxic cerebral vasoconstriction was evaluated in 7 dogs breathing room air at ambient pressure and in 5 dogs breathing 100 per cent oxygen at 2.3 atmospheric pressure Cerebral blood flow measured with the radioactive xenon clearance method, was determined serially before and after administration of 5 mg per kilogram of acetazolamide intravenously

Following the administration of acet azolamide at ambient environment the mean fast flow increased from a base-line level of 60.8 to 112 4 ml per 100 Gm per minute and slow flow from 16.2 to 24 6 ml. per 100 Gm per minute with the arterial pCO and arterial blood pressure remaining relatively constant The cerebral blood flow was markedly increased at 10 minutes, it attained a peak at 30 minutes and tended to remain elevated throughout the two hou observation period

Hyperbaric oxygenation (arterial pO = 1,548 mm Hg) reduced the mean fast flow from 66 4 to 55 9 ml per 100 Gm per minute and mean slow flow from 17.2 to 15 3 ml per 100 Gm per minute. Administration of acetazolamide during hyperbaric oxygenation raised the mean fast flow to 134 8 and slow flow to 24 7 ml per 100 Gm per minute This increase of cerebral blood flow was not observed in the 3 con trol animals which were subjected to only hyperbaric oxygenation without receiving acetazolamide.

These studies demonstrate that azolamide in a small amount effectively counteracts the ce

constricting effect of hyperoxia but also significantly increases cerebral blood flow at both ambient and hyperbaric conditions.

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Table III Cerebral blood flow data submitted for statistical analysis

Group	Fast flow (ml./100 Gm./min.)					Slow flow (ml./100 Gm./min.)				
	1	2	3	4	5	6	7	8	9	10
	Time after acetazolamide					Time after acetazolamide				
	Control 1	Control 2	10 min	30 min	60 min.	Control 1	Control 2	10 min	30 min.	60 min
Group I										
Dog 1	61 6	57 4	83 5	80 0	97 3	10 7	10 9	17 0	14 2	17 1
Dog 2	61 2	68 2	105 0	100 2	92 1	18 0	19 8	18 6	19 5	19 9
Dog 3	59 6	52 8	84 4	86 9	77 6	17 6	10 2	14 8	19 9	18 7
Dog 4	60 9	66 1	141 2	135 5	107 6	19 5	19 7	28 9	30 3	[illegible]
Dog 5	58 0	69 1	157 2	181 9	181 4	12 5	16 2	23 4	39 7	30 9
Dog 6	56 9	56 0	74 5	67 2	67 2	14 3	14 9	18 7	18 1	21 7
Dog 7	65 0	58 3	114 1	135 1	99 0	22 3	19 6	33 5	30 2	20 0
Group II										
Dog 8	61 5	53 6	136 4	146 4	128 9	17 5	17 0	23 6	25 8	19 1
Dog 9	94 2	85 3	71 9	95 4	88 6	17 9	18 6	13 8	19 0	19 9
Dog 10	58 3	70 3	103 7	127 3	96 0	13 1	19 7	23 8	27 1	17 0
Dog 11	48 4	54 6	185 7	210 8	184 0	15 4	16 2	18 3	31 6	19 9
Dog 12	69 5	68 2	91 1	94 4	117 0	22 0	14 5	22 2	20 0	1 0
*Group III**										
Dog 13	61 7	59 3	47 7	51 9	69 4	11 5	17 3	14 0	15 2	15 5
Dog 14	58 3	64 1	37 8	39 3	43 4	12 9	14 1	10 2	8 3	[illegible]
Dog 15	50 8	53 4	45 2	34 0	40 7	17 2	16 0	20 7	11 3	11 9

*No acetazolamide was given in this group.

Appendix

Statistical considerations In Table III the values for fast and slow cerebral flow in each of the two control periods and at 10 30 and 60 minutes after administration of acetazolamide in Groups I and II are combined with the observations made at comparable times in the Group III controls. For purpose of analysis, the data in Table III comprised the observation matrix for a multivariate analysis of variance,[1] which was carried out with the help of a digital computer The linear model used is expressible in the form of the matrix equation

$$E\,[Y] = [A]\ \ [B]$$

where the symbol E, is the expectation operator and $[Y]$ is the data of Table III displayed as a matrix. $[A]$ is the design matrix whose transpose is

$$[A]^T = \begin{bmatrix} 1111111 & 00000 & 000 \\ 0000000 & 11111 & 000 \\ 0000000 & 00000 & 111 \end{bmatrix}$$

and $[B]$ is the matrix of parameters

$$\begin{bmatrix} \alpha_{1} & \alpha_{1,2} & \alpha_{1,3} & \alpha_{1,4} & \alpha_{1,5} & \vdots & \beta_{1} & \beta & \beta_{1,} & \beta & \beta_{1,10} \\ \alpha_{2,1} & \alpha_{2} & \alpha_{2,3} & \alpha_{2,4} & \alpha_{2,5} & \vdots & \beta_{2} & \beta_{2} & \beta_{2,3} & \beta_{2} & \beta_{2,10} \\ \alpha_{3,1} & \alpha_{3,2} & \alpha_{3} & \alpha_{3} & \alpha_{3} & & \beta_{3} & \beta & \beta_{3} & \beta & \beta_{3} \end{bmatrix}$$

α_{ij} and β_{ij} representing the mean values for fast and slow blood flow respectively in the i[th] Group (i = 1 2 and 3) and the j[th] column of Table III In order to assess whether the cerebral blood flow values in columns 3 to 5 or 8 to 10 of Table III were significantly different from those in columns 1 to 2 or 6 to 7 respectively the composite hypothesis

$$\begin{bmatrix} 1\,0\,0 \\ 0\,1\,0 \\ 0\,0\,1 \end{bmatrix} [B] \begin{bmatrix} 3 & 0 \\ 3 & 0 \\ -2 & 0 \\ -2 & 0 \\ -2 & 0 \\ 0 & 3 \\ 0 & 3 \\ 0 & -2 \\ 0 & -2 \\ 0 & -2 \end{bmatrix} = [0],$$

was tested and rejected at the 1 per cent level. Examination of the contrasts in the individual treatment groups indicated that the significant changes were, as expected increases of flow (both fast and slow) in Groups I and II with a suggestive decrease n Group III Using premultiplication by a different contrast matrix

$$\begin{bmatrix} 1 & -1 & 0 \\ 1 & 0 & -1 \end{bmatrix}$$

and the same postmultiplying matrix as above it was possible to compare the changes in flow among the three treatment groups this comparison revealed a significant difference between the response in Group I and that in the controls of Group II ($p < 0.05$) but only an equivocal difference between the responses to acetazolamide in ambient and hyperbaric environments ($p < 0.1$)

Cardiovascular response of hypoxic myocardium to acetyl strophanthidin

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Although the effects of hypoxia and of digitalis preparations on cardiac dynamics have been studied by many workers,[1] little has been reported concerning the effect of digitalis glycosides on hypoxic myocardium. Therefore, it was felt that the results of a study of the effects of acetyl strophanthidin on an acutely hypoxic myocardium might be of some interest. The present paper reports hemodynamic changes of the heart and peripheral arteries in response to acetyl strophanthidin given to intact dogs with hypoxic myocardium.

Methods

Ten mongrel dogs weighing 9 to 20 Kg. were studied. Each dog was anesthetized with sodium pentobarbital (30 mg. per kilogram intravenously) and intubed with a cuffed endotracheal tube. The dog was ventilated on room air using a Harvard ventilator set at a frequency of about 10 cycles per minute and a tidal volume of approximately 250 to 300 ml. per cycle. Incisions were made to expose both right and left femoral arteries and the left jugular vein. A polyethylene catheter was inserted into the aorta via the left femoral artery and attached to a Statham pressure transducer to record mean and phasic aortic pressure. Under fluoroscopic guidance an end-hole Teflon catheter was passed retrograde from the right femoral artery into the left ventricle. The catheter was also connected to a Statham pressure transducer to record left ventricular pressure. A polyethylene catheter placed in the left jugular vein was used as an injection site for indocyanine green (Cardio-green) and acetyl strophanthidin.

The experiment consisted of three periods: a 30 minute control period on room air, followed by the 45 to 60 minute hypoxic period, and finally a 20 minute recovery period on room air. The dogs were made acutely hypoxic by inhalation of either 7 or 10 per cent oxygen in nitrogen through a cuffed endotracheal tube. Acetyl strophanthidin (0.025 mg. per kilogram) was given intravenously after a period of [illegible] minutes of acute hypoxia.

In each experiment the following param-

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eters were measured before, during and after the administration of acetyl strophanthidin cardiac output, aortic and left ventricular pressures, rate of change of left ventricular pressure (LV dp/dt) Lead II electrocardiogram arterial blood samples for pH pO_2, pCO_2, and oxygen saturation The blood oxygen content values were determined by the Van Slyke manometric method and the pH pO_2 and pCO were measured by Instrumentation Laboratory electrodes. Cardiac output was measured by indicator-dilution techniques described in a previous paper [6]

In addition to the above mentioned parameters, calculated values for stroke volume left ventricular stroke work, and total systemic resistance were obtained according to the standard formulas.

In three additional animals left ventricular pressure was measured simultaneously through the catheter as well as through a No 15 rigid large-bore vinyl tubing inserted percutaneously into the left ventricle in order to compare the left ventricular pressure contour and the LV dp/dt. The LV dp/dt recorded as millimeter amplitude of the wave-form deflection was obtained electronically through an R C differentiating circuit with a time constant of 4.4×10^{-4} sec.

Results

As shown in Fig 1 the left ventricular pressure tracings obtained through the catheter and the rigid tubing compare favorably The directional and magnitude changes of the LV dp/dt are almost identi-

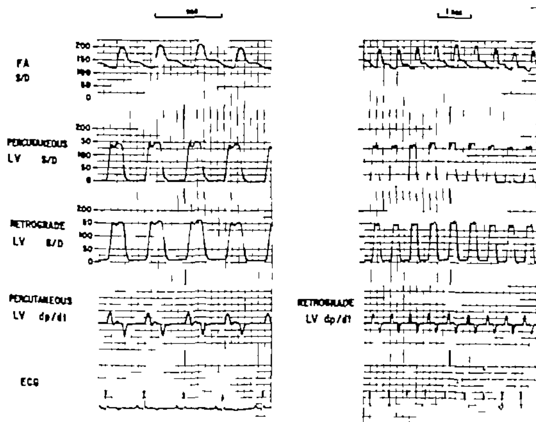


Fig 1 Simultaneous recording of the femoral arterial pressure (*FA S D*), left ventricular pressure (*LV S D*) rate of change of left ventricular systolic pressure (*LV dp dt*), and electrocardiogram (*ECG*) in dog The upper tracing of the left ventricular pressure obtained through stiff tubing inserted percutaneously into the left ventricle, while the lower tracing was obtained through retrograde catheter The *LV dp dt* on the left panel was recorded through the percutaneous route, whereas the *LV dp/dt* on the right panel through the retrograde catheter Note the similarity of the pressure tracing and the identical magnitude of the *LV dp/dt*.

cal. The similarities have been demonstrated in a previous publication, and indicate that the catheter-gauge system gave a reliable reproduction at least qualitatively of left ventricular pressure and the directional change of LV dp/dt.[11]

The hemodynamic data are presented respectively in Tables I to III. When measured values are entered for control, hypoxia, maximum drug responses, and recovery phases of each experiment. In order to use each dog as its own control, the results are expressed as per cent change of the parameters in response to the effects of hypoxia or of acetyl strophanthidin.

The average per cent of blood oxygen saturation for the control phase was 95 per cent. During the hypoxic phases arterial

Table I. Effects of acute hypoxia and acetyl strophanthidin

Dog no. (wt in Kg)	*Period of study*	*pH*	*pCO_2 (mm Hg)*	*pO_2 (mm Hg)*	*% Saturation*	*C.O. (L/min)*	*H.R. (beats/*
2	Control	7.26	57	51	84.5	1.78	113
(14)	Hypoxia	7.36	55	41	76	1.73	105
	Ac. St.	7.35	49	43	78	1.66	105
	Recovery	7.29	56	79	95	1.39	109
4	Control	7.53	28	114	96	1.19	154
(14)	Hypoxia	7.50	26	42	78	1.25	141
	Ac. St	7.53	22.5	44	77.5	1.56	139
	Recovery	7.49	22	102	99	1.10	144
5	Control	7.34	47	76	96.5	2.05	133
(16)	Hypoxia	7.40	34	36	70	2.35	136
	Ac. St.	7.42	29	45	80	NM	136
	Recovery	7.33	50	75	94	1.48	136
6	Control	7.40	32	85	95.5	1.68	139
(17)	Hypoxia	7.59	22	47	82	1.21	145
	Ac. St.	7.55	18	45	86	1.17	119
	Recovery	7.48	19.5	101	97	NM	149
7	Control	7.37	36.5	91.8	96.3	1.70	167
(20)	Hypoxia	7.45	30.8	33.7	65.5	1.32	136
	Ac. St.	7.42	31	33.8	65.3	1.55	139
	Recovery	7.34	33	98	96.9	1.13	141
8	Control	7.53	23	107	97.6	1.49	172
(18)	Hypoxia	7.62	17	33.5	64	1.76	167
	Ac. St.	7.57	15	27	51	1.69	157
	Recovery	7.48	19	68	92.4	1.97	158
9	Control	7.29	46	81.6	95.2	1.90	148
(16)	Hypoxia	7.48	47	34.6	66.5	2.00	158
	Ac. St.	7.40	38	22.1	40	2.21	160
	Recovery	7.36	35	90.9	96.2	1.48	136
10	Control	7.36	36	74.5	94.2	2.17	143
(11)	Hypoxia	7.52	28	33.2	64	2.34	154
	Ac. St.	7.31	25	29.5	57	2.34	150
	Recovery	7.39	33	75	94.4	1.50	144
12	Control	7.43	35	93	96.4	1.43	157
(12)	Hypoxia	7.51	33	40	74.5	1.94	NM
	Ac. St	—	—	—	—	NM	—
	Recovery	—	—	—	—	NM	—
12	Control	—	—	—	—	NM	—
(12)	Hypoxia	7.44	33	36	69	1.53	—
	Ac. St	—	—	—	—	NM	—
	Recovery	7.38	37	66	92	1.19	—

Abbreviations: pCO_2 Arterial CO_2 tension; pO_2 arterial O_2 tension; C.O., cardiac output; H.R., heart rate; S.V., stroke volume; S/D systolic/diastolic; T.S.R., total systemic resistance; Ac. St., acetyl strophanthidin; N.M. not measured.

oxygen saturation ranged from 82 to 64 per cent (average 71 per cent)

The dosage of acetyl strophanthidin used produced no demonstrable toxic effects.

Response to hypoxia alone.

HEART RATE. Hypoxia resulted in changes in the heart rate ranging from +13 to −18.5 per cent (average −2 per cent) of control values.

CARDIAC OUTPUT The changes in cardiac output varied from +35 to −28 per cent (average +4 per cent) of control values.

LEFT VENTRICULAR STROKE WORK. The left ventricular stroke work tended to increase slightly although two dogs did show a decrease. The changes ranged from +25 to −18 per cent (average +8 per cent) of control levels.

S.V. (ml/beat)	S.W. (gmM/beat/Kg)	L.V. (mm. Hg)	dp/dt	Aortic blood pressure (mm. Hg) S/D	Aortic blood pressure (mm. Hg) Mean	T.S.R. (units)
15 5	147	126/0	6	125/76	93	4 2
16 5	168	140/0	7 2	140/85	100	4 6
15 8	185	148/0	8 8	150/95	115	5 5
13 9	133	125/0	8 0	123/78	94	5 4
7 7	74 5	125/4	10	120/80	95	6 4
8 75	87	115/5	9	115/85	97	6 2
11 3	129	137/5	11	137/105	112	5 7
7 55	62	106/3	8 5	107/75	80	5 8
15 4	186	190/10	13	180/125	135	5 2
17 3	232	225/0	16	195/135	150	5 1
—	—	260/0	19	230/148	165	—
10 9	117	190/5	14	145/110	120	6 5
11 2	113	146/7	10 5	146/110	120	5 7
8 35	93	155/0	10 5	155/120	132	8 7
10 6	150	190/0	13	185/135	145	9 9
—	—	182/0	9 5	175/125	140	—
10 2	80	136/0	14	135/90	110	5 2
9 7	75	95/0	10 5	132/100	108	6 5
11 9	125	120/0	13 5	170/135	145	7 7
7 9	51	105/0	8	105/80	90	6 4
8 65	86	170/0	13 5	150/110	125	6 7
10 8	104	155/5	11	155/115	125	6 7
9 0	128	220/10	11	220/150	180	8 5
12 4	113	—	—	—	115	4 6
13 6	152	NM	NM	NM	125	5 2
12 6	152	170/0	19	175/115	135	5 4
13 8	179	180/0	28	190/125	145	5 2
10 9	102	136/0	14 5	140/95	105	5 7
15 2	204	220/0	11	210/140	160	5 9
15 2	217	220/10	10	200/153	170	5 8
15 6	288	270/10	12	270/190	220	7 5
11 2	146	225/0	8	200/140	155	8 3
7 7	128	190/0	15	190/125	140	7 8
—	—	225/0	20	200/130	150	6 2
—	—	240/0	21	220/120	160	—
—	—	175/0	14	160/105	125	—
—	—	175/0	14	160/105	125	—
—	—	205/0	18	180/110	140	7 3
—	—	245/5	26	220/125	160	—
—	—	187/0	14	156/115	125	8 4

stroke work; L.V., left ventricular pressure; dp/dt, rate of change of L.V. pressure, as millimeter amplitude of wave-form deflection

Table II Response to acute hypoxia (expressed as per cent change from control)

Dog no	H.R.	C.O	S V	Left ventricl		M.A.P	T.S.R.
				S H	dp/dt		
2	−9	−3	+6	+14	+20	+7	+11
4	−7	+5	+13	+17	−10	0	+3
5	+2	+14	+13	+25	+23	+11	−3
6	−3	−28	−25	−18	0	+10	+53
7	−18	−22	−5	−7	−25	0	+13
8	−3	−18	+21	−21	−18	9	−13
9	+13	+5	−7	0	—	+8	+3
10	+8	+8	0	+6	−9	+6	0
12	—	+35	—	—	+30	+7	−20
Average	−2	+4	+2	+8	+5	+6	+5

The above symbol and bbreviations are the same as hose used in T ble L.
*M.A.P Mean aortic pressure.

Table III Response to acute digitalisation during hypoxia (expressed as per cent change from hypoxic period)

Dog no	H R	C O	S V	Left ventricle		M A.P	T.S.R.
				S H	dp/dt		
2	0	−4	−4	+10	+22	+15	+20
4	−3	+25	+29	+48	+22	+16	−8
5	—	—	—	—	+19	+10	—
6	−24	−3	+27	+40	+24	+10	+15
7	−5	+16	+23	+65	+29	+32	+17
8	+12	−4	−14	+23	0	+44	+19
9	0	+11	+9	+16	+47	+9	−3
10	−2	0	+3	+33	+20	+29	+29
12	—	—	—	—	+44	+14	—
A erage	−3	+6	+10	+34	+25	+20	+17

The abov symbols and abbreviations are the same as those used in T bles I and II.

MEAN AORTIC PRESSURE The mean aortic pressure rose in the majority of the dogs, showing changes ranging from +11 to 0 (average +6 per cent) of control levels.

TOTAL SYSTEMIC RESISTANCE. There was some variability in total systemic resistance ranging from +53 to −20 per cent (average +5 per cent) of control levels.

RATE OF CHANGE OF LEFT VENTRICULAR PRESSURE (DP/DT) The changes in LV dp/dt ranged from +33 to −25 per cent (average +5 per cent) showing no consistent re-sponse from control values.

Response to acetyl strophanthidin under hypoxic conditions These represent maxi-mum changes observed following adminis-tration of the drug usually occurring 3 to 5 minutes after the end of the infusion.

HEART RATE. The animals responded to the acetyl strophanthidin by decrease in heart rate in 4 cases, no change in 2, and increase in 2 The changes ranged from +12

to −24 per cent (average −3 per cent) of levels before acetyl strophanthidin.

CARDIAC OUTPUT The cardiac output changes were variable but tended to show increases. The cardiac output response ranged from +25 to −4 per cent (average +6 per cent) of hypoxic levels.

LEFT VENTRICULAR STROKE WORK. The animals responded to the drug with an increase in stroke work ranging from +65 to +10 per cent (average +34 per cent) of hypoxic levels, with little or no change in the left ventricular diastolic pressure.

MEAN AORTIC PRESSURE. There was a uniform increase in mean aortic pressure this increase ranged from +44 to +9 (average +20 per cent) of hypoxic values.

TOTAL SYSTEMIC RESISTANCE In 5 of the 7 animals in which it was calculated there was an increase in total systemic resistance The overall changes ranged from +49 to −8 per cent (average +17 per cent)

LEFT VENTRICULAR DIASTOLIC PRESSURE. No consistent change in the left ventricular diastolic pressure was observed

RATE OF CHANGE OF LEFT VENTRICULAR PRESSURE. In most cases there was a significant increase in LV dp/dt. The animals showed changes ranging from +47 to 0 per cent (average +25 per cent) of hypoxic levels.

Discussion

Cardiac response in systemic hypoxemia is the resultant outcome of the complex interaction of direct and reflex factors. Previous workers have shown that central nervous system and adrenal hypoxia as well as the direct effect of hypoxia and acidemia on myocardium and blood vessels are important determinants.[11] On the average there was a tendency toward increased LV dp/dt and cardiac output Although in the present study the average increase in cardiac output was only +4 per cent, 6 of the 9 animals had an average rise of 12 5 per cent in keeping with previously published data.[12, 13] The change in aortic pressure was rather insignificant. The stroke work increased an average of 8 per cent during hypoxia. Kahler and associates demonstrated that although the direct effect of hypoxia causes a lower total systemic resistance and decreased stroke work a chemoreceptor reflex during hypoxia produces the observed slight rise in total systemic resistance and stroke work.

Previous workers have demonstrated that digitalis preparation definitely augments the myocardial contractility and function in normally oxygenated animals.[4-8] In the present study the consistent increase in LV dp/dt (+25 per cent) and in left ventricular stroke work (+34 per cent) without significant change in left ventricular end-diastolic pressure after administration of acetyl strophanthidin during acute hypoxia would imply a positive inotropic effect of the drug on the hypoxic myocardium This positive inotropic effect, however is less than the 89 per cent increase in LV dp/dt noted by Braunwald and associates,[9] when nonhypoxic cardiac patients were given a 0 025 mg per kilogram intravenous dosage of acetyl strophanthidin Furthermore in three nonhypoxic animals given 0 025 mg per kilogram of acetyl strophanthidin intravenously average increases of 48 per cent in stroke work and 84 per cent in LV dp/dt were noted respectively Apparently under conditions of hypoxia the acetyl strophanthidin effect on cardiovascular dynamics is attenuated This could in part be due to a less responsive myocardium or possibly to the fact that there has already been some positive cardiac response to the hypoxia.

In order to demonstrate that the effect of the acetyl strophanthidin on the hypoxic myocardium was not fully dependent on catecholamines, experiments were undertaken using three animals pretreated with intravenous propranolol (1 mg per kilogram) Propranolol has been shown to be a specific blocker of beta-adrenergic activity but does not interfere with the actions of cardiac glycosides on the myocardium [4, 1] Comparing the performance of hypoxic myocardium before and after beta-adrenergic blockade the acetyl strophanthidin is no less effective after blockade than before LV dp/dt increased +28 per cent without beta adrenergic blockade and +31 per cent after pretreatment with propranolol. Thus, the presence or absence of beta-adrenergic blockade has little or no effect on the response of the hypoxic myocardium to acetyl strophanthidin The ability of the hypoxic myocardium to respond to acetyl strophanthidin stimulation after adequate beta

adrenergic blockade indicates that the effects observed are not a result of secondary epinephrine release due to the hypoxia. Furthermore, since acetyl strophanthidin was given during a relatively steady state and the average arterial desaturation was only 63 per cent significant epinephrine release from the adrenals would not be expected.[19]

The smooth muscle of the peripheral vessels also responded to the acetyl strophanthidin with an average increase of 17 per cent in total systemic resistance. The presence of a definite increase in total systemic resistance in these animals suggests a vasoconstrictive effect of acetyl strophanthidin on peripheral vessels similar to that previously demonstrated by Ross and associates.[5] This vasoconstriction following administration of acetyl strophanthidin accentuated the vasoconstrictive response to hypoxia in intact animals. This response may partly contribute to the slight increase in the stroke work.

Summary

Generalized acute hypoxia (average 71 per cent of O_2 saturation) in intact dogs resulted in a slight increase in the rate of change of the left ventricular pressure (LV dp/dt) left ventricular stroke work (LV_{sw}) and total systemic resistance. This response was similar to that reported by other workers.

A positive inotropic effect of acetyl strophanthidin was demonstrated on the hypoxic myocardium as reflected by a consistent increase in LV dp/dt and LV_{sw} associated with no significant change in the left ventricular end-diastolic pressure. This effect was not altered by beta adrenergic blockade. Acetyl strophanthidin however exerted an appreciably greater inotropism on the nonhypoxic myocardium than on the hypoxic myocardium.

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Case reports

Calcified atrial myxoma: Diagnostic significance of the "systolic tumor sound" in a case presenting as tricuspid insufficiency

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The preoperative diagnosis of an atrial myxoma was made first by Goldberg and associates[1] in 1952 by venous angiography. Interest in this tumor has grown rapidly since the first reported successful surgical removal of a left atrial myxoma by Crafoord in 1955,[2-4] but consistent clinical recognition remains very difficult. Right atrial myxomas may closely mimic and be readily confused with various disorders such as Ebstein's anomaly, bacterial endocarditis, constrictive pericarditis, and rheumatic heart disease with tricuspid stenosis.[5-6] Severe tricuspid insufficiency as the presenting hemodynamic disturbance is unusual.[7,8] Unique physical and radiological signs are uncommon in the diagnosis of atrial myxomas and a high degree of clinical suspicion supplanted by specialized diagnostic methods such as venous angiography is necessary if early clinical diagnosis is to be made.

The present report describes a case of a successfully excised calcified right atrial myxoma which had completely destroyed the tricuspid valve and presented as tricuspid insufficiency. It is of particular interest because of the documentation of a newer auscultatory finding believed to be unique for an atrial tumor. In addition the previously unemphasized value of fluoroscopy in recognizing a calcified tumor is demonstrated. Further information on the relationship of tumor calcification to tricuspid insufficiency and its role in clinical diagnosis is gained from a review of the literature.

Case report

G. L.,† a 60-year-old white woman, was in good health until two years prior to admission, at which time she noted the insidious onset of malaise, weakness, anorexia, and weight loss. One and one half years prior to admission she experienced ankle edema and progressive dyspnea on exertion. She denied

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episodic dyspnea, chest pain, or hemoptysis. There was no orthopnea, paroxysmal nocturnal dyspnea, cough, dizziness, syncope, chills, or fever. There was no history of a heart murmur or rheumatic fever. Because of increasing symptoms she was hospitalized elsewhere and treated for congestive heart failure with digoxin and ethacrynic acid. The shortness of breath improved and the peripheral edema diminished but weakness and malaise increased. An intracardiac mass felt to be tumor was noted on radiological examination and the patient was transferred to Georgetown University Hospital for further evaluation.

On physical examination she appeared chronically ill but in no respiratory distress. The blood pressure was 160/90 mm. Hg, the pulse was 85 beat per minute and regular. Rectal temperature 99.4° F. The skin was noncyanotic, warm, and dry. Carotid and peripheral pulses were normal, pulsus paradoxus being absent. Mean jugular venous pressure was elevated to 5 cm. above the clavicle in the sitting position and respiratory variation was not discernible. A and V waves were both prominent. The apical impulse, interpreted as left ventricular, was palpated in the fifth left interspace in the anterior axillary line. There was minimal systolic lift along the lower left sternal border. The first sound was of normal or diminished intensity and the second sound was single. Following the first sound and dominating early systole was a loud popping or snapping sound heard best along the lower left sternal border (Fig. 2, X_2). Variation in intensity was present but did not correlate with positional change or with the respiratory cycle. In late diastole there was a readily audible sound which resembled an atrial gallop but was more abrupt (Fig. 2, X). A Grade III/VI pansystolic murmur and a Grade II/VI late diastolic rumble were heard along the lower left sternal border. The diastolic rumble built up to tumor sound (X) and subsided prior to the first sound (S_1). The liver edge extended to 6 cm. below the right costal margin and by percussion had a 14 cm. span. There was no peripheral edema. Neurological examination was unremarkable.

Laboratory values were as follows: Hematocrit, 4[illegible] per cent; W. B. C., 6,600 with 61 neutrophils, [illegible], and 27 small lymphocytes; platelets, normal. The corrected sedimentation rates averaged 17 mm. per hour. Serum proteins by electrophoresis showed total, 7.1 Gm. per cent; albumin, 3.44 Gm. per cent. Globulins were distributed as: γ 1.22 Gm. per cent, β 1.18 Gm. per cent, α_2 0.80 Gm. per cent, α_1 [illegible] Gm. per cent. Urinalysis showed a trace of albumin. Bromsulphalein 34 per cent retention in 45 minutes. Total blood volume was 5,120 ml. (calculated normal, 4,140 ml.). The following were within normal limits: prothrombin time, free blood sugar, blood urea nitrogen, serum creatinine, sodium, chloride, potassium, and carbon dioxide. First degree A-V block and a right bundle branch block were noted on the electrocardiogram. Chest x-rays showed normal lung fields and an over-all increase in heart size. Overpenetrated views failed to demonstrate an intracardiac mass. However on cinefluoroscopy a calcified mass of approximately 7 by 4 cm. diameter was clearly visualized swinging and twisting into the right atrium during each ventricular systole and into the ventricle in diastole.

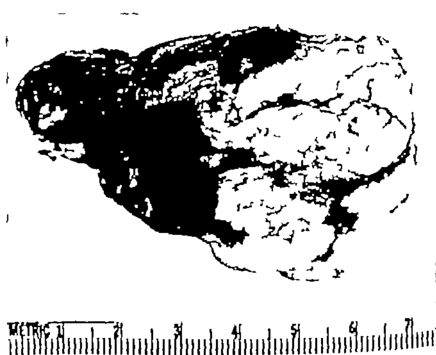


Fig. 1. Gross appearance of tumor. Note gelatinous appearance of [illegible] area and large area of calcification.

On right heart catheterization, the right atrial pressure tracing showed V waves measuring 18 mm. and A waves of 17 mm. Mean RA pressure was 10 mm. Hg Right atrial cineangiography confirmed the fluoroscopic impression of calcified atrial tumor which appeared to be attached to the interatrial septum. Movement of the catheter tip into the right ventricular cavity precipitated multiple premature ventricular contractions and interfered with tumor movement between the two chambers. Arterial oxygen saturation was 98.5 per cent.

With the preoperative diagnosis of calcified right atrial myxoma, surgery was performed under cardiopulmonary bypass. A pedunculated mass measuring about 4 cm. across was found attached to the atrial septum above the area of the fossa ovalis (Fig. 1). The tumor was removed by sharp dissection, necessitating creation of 2 cm atrial septal defect which was closed with running suture. The posterior mural and anterior septal leaflets of the tricuspid valve were completely destroyed by the tumor. The destroyed valve was resected and replaced with 22 mm. Hufnagel discoid valve. Following an uncomplicated postoperative course she was discharged from the hospital on the twelfth postoperative day. On follow-up visits, now 24 months following surgery she has continued to do well. A follow-up phonocardiogram (Fig. 3) confirmed disappearance of the murmur and the presence of tricuspid prosthetic valve sounds. The findings on pathological examination were consistent with the diagnosis of calcified myxoma.

Discussion

Although the etiology of atrial myxomas is unknown they are generally considered to be neoplastic rather than thrombotic in origin.[7,10] About one fourth occur on the septum of the right atrium and three fourths on the left.[11] They are slightly more common in women[12] and the mean patient age is about 45 years.[4,12] Symptoms may be due to valvular obstruction or insufficiency peripheral or pulmonary embolism of tumor fragments, or to systemic effects as manifested by malaise, fatigue, fever and weight loss. Laboratory findings of anemia, elevated sedimentation rate and serum protein abnormalities may be present in addition.[7,12] The physical findings of atrial myxomas cover a broad spectrum and are reviewed elsewhere. Systolic and diastolic murmurs may mimic those of

Description kindly supplied by Dr William F. Manion.

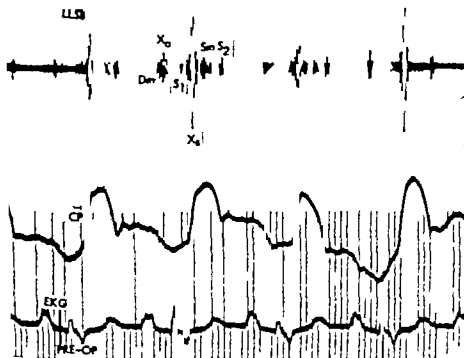


Fig. 2. Preoperative phonocardiogram. Systolic tumor sound (X_s) follows first sound (S_1). Diastolic tumor sound (X_d) follows diastolic murmur (DM) and atrial contraction. Systolic murmur (SM) carries through to second sound (S_2). Carotid pulse (CP) is also shown.

other forms of congenital or acquired heart disease. Opening snaps, atrial diastolic gallops, and ventricular diastolic gallops have been described.[14,17] Certain findings, however, are highly suggestive of an atrial tumor. These include severe hypotension and tachycardia caused by turning the supine patient to one side or the other, or a diastolic rumble which is accentuated in the upright position and which may actually disappear in the supine position.[17]

The present case demonstrated an additional auscultatory finding believed to be caused by tumor movement and therefore unique for an intracardiac tumor. This was an early systolic extra sound X (Fig. 2) heard along the lower left sternal border (LLSB). It was popping rather than clicking in quality and its intensity was variable. Variation or disappearance of the sound with positional changes could not be demonstrated. On the phonocardiographic record it was noted to follow the QRS onset by .15 to .18 sec. and the first sound (S_1) by .04-.06 sec. This sound had neither the timing (occurring later) nor the clicking quality of a pulmonary or aortic ejection click. It has been referred to previously as a tumor ejection sound, and was shown in a case of a left atrial myxoma to be caused by systolic propulsion of the tumor from the ventricle to the atrium. It was associated with a notch and change in slope of the left ventricular pressure curve.[18] Unfortunately, in the present case we were unable to satisfactorily record the right ventricular pressure curve due to marked irritability when the catheter was advanced to the right ventricle. The presence of this systolic tumor sound should lead to a strong suspicion of the correct diagnosis. In addition, there was a pre-systolic sound with the timing of an atrial diastolic gallop (ADG), but more abrupt in

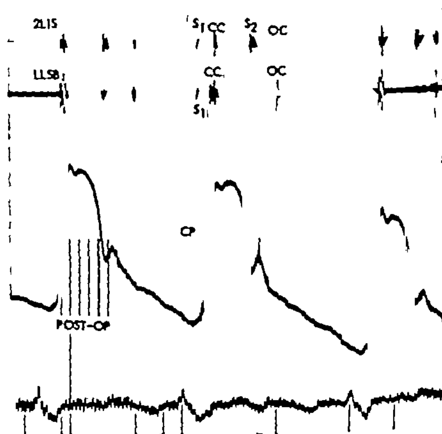


Fig. 3. Postoperative phonocardiogram. Closing click of prosthetic valve (*CC*) and opening click of prosthetic valve (*OC*) recorded along lower left sternal border (*LLSB*) and second left intercostal space (*2LIS*). For other abbreviations see Fig. 2.

character. This sound was apparently due to atrial propulsion of the tumor into the ventricle during atrial contraction. A similar sound was described in a case of an ossified right atrial myxoma which had completely destroyed the tricuspid valve.[4]

On chest x-ray we were unable to identify the calcified tumor despite obtaining overpenetrated films with PA, lateral and oblique views. However, on fluoroscopy the calcified tumor with its rather dramatic swinging and twisting motions, was immediately obvious. Others have also reported visualization of calcified myxomas by fluoroscopy which were not noted on x-ray (Table I). This does not imply that calcified myxomas are never seen on chest x-rays, but rather brings out a diagnostic point not previously emphasized—that the presence of calcium in an atrial myxoma may afford a unique diagnostic opportunity if properly sought by fluoroscopy. Failure to demonstrate the calcified mass on x-ray may be due to rapid tumor movement at the moment the x-ray was taken.

Tricuspid insufficiency rather than tricuspid stenosis appears to be the predominant hemodynamic disturbance in cases of calcified right atrial myxoma. In 6 of 8 cases in which the hemodynamic disturbance was mentioned, significant tricuspid insufficiency was present (Table I). Presumably this is caused by the "wrecking ball" effect which the calcified or ossified tumor produces, simulating the large swinging iron ball connected by a large chain to a high crane used to demolish large buildings."*[22] In addition, it appears as if calcified tumors have been present for a greater length of time. In one case, calcification had been present for 37 years and the mean duration of symptoms was 7.4 years. In noncalcified myxomas, symptoms have usually been present for a shorter period of time.

We know of no previous cases of successful replacement of a tricuspid valve destroyed by an atrial myxoma by a prosthetic valve.

*Term used by W. Proctor Harvey, M.D. See reference 22.

Table I. Résumé of reviewed cases of calcified right atrial myxomas

Author and year	*Patient sex and age (yr.)*	*Duration of symptoms (yr.)*	*Hemodynamic findings*	*Comments*
Bahnson, et al.[illegible] (1954)	F 54	6	Tricuspid insufficiency	Diagnosed by angiography
Buenger, et al.[illegible] (1955)	M 16	4	Tricuspid insufficiency	Tumor diagnosed by fluoroscopy; histologically contained rhabdomyomatosis elements
Ellis, et al. (1958)	M 48	4	*Free tricuspid insufficiency	Diagnosis at surgery
Hopkins, et al.[illegible] (1958)	M 26	Several	—	Pendulum movement noted on fluoroscopy
Kudlikova, et al.[illegible] (1958)	F 14	8	Tricuspid insufficiency	Swinging plum-sized mass noted on fluoroscopy but not on x-ray
Brown[4] (1963)	F 38	13	Tricuspid obstruction	Calcium seen on fluoroscopy but diagnosis made at surgery
Wight, et al.[illegible] (1963)	M; 23	—	Tricuspid obstruction	Moving calcified mass seen on fluoroscopy but not on x-ray
Oliver, et al. (1966)	M 63	15	Tricuspid insufficiency	Tumor ossified; tricuspid valve completely destroyed. Surgery unsuccessful
Present case (1967)	F 60	3	Tricuspid insufficiency	Destroyed valve successfully replaced with prosthesis

Summary

A calcified right atrial myxoma presenting as tricuspid insufficiency was successfully excised and the destroyed valve replaced with a prosthesis. The case is presented to illustrate two useful but previously unemphasized diagnostic features. (1) A systolic tumor sound distinctive both in timing and quality was identified (2) *Calcification* was shown to have additional diagnostic value when properly sought by fluoroscopy in addition to routine x ray examination

A review of the literature suggests that tricuspid insufficiency is the predominant hemodynamic disturbance in cases of right atrial myxomas which are grossly calcified This otherwise lethal tumor is surgically curable if diagnosed early

The authors wish to thank Dr Bernard Walsh for referring this patient and credit him and Dr Hans Schneider with having appreciated the tumor on standard fluoroscopy

The authors also acknowledge the support of Dr Joseph F LeBauer and Miss Rosemary Glasheen R N in the Cardiac Diagnostic Laboratory

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Origin of a single coronary artery from the pulmonary artery

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Anomalous origin of a coronary artery from the pulmonary artery is an infrequent variation of the coronary vascu lature. The left coronary artery is affected most frequently while anomalous origin of the right coronary artery or both coronary arteries from the pulmonary trunk are rare lesions.

In a case study of congenital anomalies of the coronary arteries, a patient was found with a single coronary artery supply ing the heart. This single coronary artery arose from the pulmonary artery rather than from the aorta. Only three similar cases were found in the literature

Case report

B. G. C., 6-day-old Negr female was the product of an uneventf l, full-term pregnancy Physical examination shortly after birth as normal, with no cardiac murmurs heard. On the third day of lif Grade 3/6, high-pitched holos stolic murmur developed. This was heard over the entire precor dium and back, as maximal in the second left inter costal space, and radiated to the left sternal border and left axilla. The femoral pulses ere eak and a preliminary diagnosis of aortic coarctation was made. An electrocardiogram showed right axis deviation and voltage hanges suggestive of right ventricular hypertrophy A chest -ray showed mild cardiomegaly and slightly increased pulmonary vascular markings. On the sixth day of lif she began to vomit frequently She died several hours after the onset of vomiting Resuscitative measures were unsuccessf l

The pericardial sac was dilated by clear yellow fluid The heart appeared enlarged and weighed 31 grams. The ascending aorta as pproximately two thirds the size of the pulmonary artery A large patent ductus arteriosus was present. The right trium and entricle ere slightly dilated The tricuspid and pulmonary valves ere normal. A large foramen ovale as present A large coronary ostium was found in the left pulmonary sinus. This gave rise to single coronary artery hich immediately divided into right and left branches The left coronary artery subsequentl divided into normal circumflex and anterior descending branches The right coronary artery coursed between the pulmonary artery and the aorta and then assumed a normal course of distribution in the right trio entricular groove (Fig 1). The left trium as slightly dilated. The left ventricle as slightly hypoplastic The aortic valve was small, but structurally normal. N ostia were found in the aortic coronary sinuses. Microscopic examination of the myocardium was nremarkable. N areas of infarction were noted.

Discussion

The first reported case of a single coronary artery arising from the pulmonary artery was described by Tow He discussed the heart of a 5-month-old female whose death was attributed to congestive heart failure Autopsy revealed a truncus arte riosus with the right and left pulmonary arteries arising separately from the pos-

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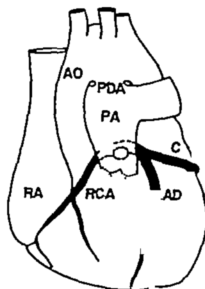


Fig. 1. Diagram of a case of a single left coronary artery originating from the pulmonary artery. See text. *AO* aorta. *PA* pulmonary artery. *RA* right atrium. *RCA* right coronary artery. *C* left circumflex coronary artery. *AD* left anterior descending coronary artery. *PDA* patent ductus arteriosus.

terior aspect of the truncus. No coronary arteries arose from the truncus. The ostium of a coronary artery was found in the left pulmonary artery just after its origin from the truncus. No ostium was seen in the right pulmonary artery. The single coronary artery was not traced distally.

Colmers and Siderides[3] described a 33-day-old male who was found dead. Autopsy revealed a severely infarcted left ventricle. No coronary ostia were present in the aorta. A large coronary ostium was found in the left pulmonary sinus. Just beyond the ostium the single coronary artery divided into right and left coronary arteries, with the right coronary artery coursing between the aorta and the pulmonary artery to reach the right atrioventricular groove. The distal branching of the right and left coronary arteries was normal.

Feldt and associates[4] described a 7 year old female who died after the correction of ventricular septal defect. She had undergone the ligation of a small patent ductus arteriosus ten months previously. Autopsy revealed no coronary ostia in the aorta. Instead a single coronary artery originated from the left pulmonary sinus. The first branch of this single left coronary artery coursed posteriorly around the aorta to become the right coronary artery. The single left coronary artery then divided into normal circumflex and anterior descending branches.

In all four cases the single coronary artery was a left coronary artery. This might be expected since the left coronary artery is usually the vessel affected when one coronary artery arises from the pulmonary artery and one arises from the aorta. Further the anomalous single left coronary artery was found in three females and one male. Anomalous origin of the left coronary artery from the pulmonary artery is found more frequently in females (2:1). The exact cause of the shift of the left coronary anlage (bud) from the aorta to the pulmonary artery during embryonic development is not known nor is the reason known why the proximal anlage (bud) of the right coronary artery failed to develop.[1,4] The coexistence of these two lesions of the coronary arteries is probably unrelated. In 112 cases of single coronary artery only four cases were found in which the single coronary artery originated from the pulmonary artery.[1] Similarly in 241 cases of anomalous origin of the left coronary artery from the pulmonary artery the left coronary artery was the sole source of myocardial blood supply in only four cases.[1]

These four cases are not only anatomically similar to anomalous origin of the left coronary artery but they are also similar from the standpoint of pathophysiology. In the case currently being reported, and in the case reported by Colmers and Siderides,[3] the myocardium was perfused by poorly oxygenated blood from the pulmonary artery. Further this blood was under a low perfusion pressure. As a result, ischemia began to occur and at a much earlier age than in anomalous origin of the left coronary artery. Colmers case had severe infarction of the left ventricle. The current case did not, probably because death occurred a few hours after symptom onset (vomiting). Survival in the cases reported by Tow[2] and Feldt and associates[4] can be attributed to the coexistent cardiovascular anomalies. The presence of the defects allowed perfusion of the single anomalous coronary artery at a high pressure. Correction of the cardiovascular defects in Feldt's case removed the sources of high pressure

in the right heart, thereby decreasing the coronary perfusion pressure and leading rapidly to the death of the patient.

The systolic murmur present in the current case was probably related to a right-to-left shunt through the patent ductus arteriosus. Unfortunately the patient died before cardiac catheterization could be performed so pressure relationships were not obtained.

Anomalous origin of a single coronary artery from the pulmonary trunk appears to be a uniformly fatal lesion in the absence of coexistent cardiac defects. Should the lesion be diagnosed the surgical approach probably should be a graft from the aorta to the transected single coronary artery similar to the grafting method used by Cooley[6] to correct anomalous origin of the left coronary artery from the pulmonary artery.

Summary

A case of a single left coronary artery originating from the pulmonary artery is presented. Three similar cases were found in the literature. These four cases are briefly discussed with regard to the anatomy and pathophysiology of the anomaly.

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Treatment of primary angiosarcoma of the heart

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Angiosarcoma of the heart, although known by many names, presents a surprisingly uniform clinical picture. Isolated case reports, as well as review articles, emphasize the frequency of chest pain, obstruction to filling of the right side of the heart, pericardial effusion, cardiomegaly, dyspnea, and hepatomegaly. The constancy of these symptoms is due to the almost invariable location of the primary tumor in the right atrium.[1-4]

A recent review of the world literature emphasized these features in tabulating 41 cases of primary myocardial angiosarcoma.[7] An additional 5 cases have been found in the literature that failed to alter the pattern of that report.[8-12] The case presented in this paper, however, lacked many of these features and initially was thought to represent recurrent idiopathic pericarditis with effusion. This is the seventh primary angiosarcoma of the heart to be diagnosed ante mortem, but only one other case was given a trial of appropriate therapy.[11] That patient had more extensive involvement at the time of initial diagnosis and eventually died of metastatic disease. Because of the early diagnosis in the case we report here, it is hoped that the therapeutic program outlined will be effective.

Case report

N. K. (UVH No. 59-02-29), a 59-year-old housewife, was in good health until September 1967, when she developed pain typical of pericarditis without other symptoms. Initially intermittent, the pain became more frequent and severe over the next two months and mild dyspnea on exertion appeared. She was seen by her local physician, who found she had a large pericardial effusion. Removal of 950 c.c. of serosanguineous fluid by pericardiocentesis brought prompt relief of symptoms. Cytologic and bacteriologic studies were negative and she was transferred to the University of Virginia Hospital.

The patient was well developed and in no distress. The presence of pericardial effusion without tamponade was confirmed by fluoroscopic demonstration of the subepicardial fat line displaced from the pericardial border. The remainder of the physical examination was normal.

The hemogram, urinalysis, sedimentation rate, several lupus erythematosus (LE) preparations, latex flocculation, serum complement, tuberculin and coccidioidomycosis, blastomycosis, and histoplasmosis skin tests, and liver function studies were normal and have remained so. An electrocardiogram showed low voltage in the limb leads and nonspecific S-T segment and T wave changes.

While in the hospital the pericardial effusion required percutaneous drainage on several occasions, despite the institution of corticosteroid therapy. The character of the fluid was unchanged, and repeated cytologic studies were nondiagnostic. Because of the recurrence of the pericardial fluid, a pericardiectomy was done in January 1968, by Dr. Gardner Smith. The pericardium was [illegible]

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Fig. 1 The opened pericardium revealing cystic, friable tumor mass involving the great vessels, pericardium, and right atrium.

Fig. 2. Photomicrograph showing vascular channels filled with thrombus and surrounded by more cellular aspects of the tumor. (Hematoxylin and eosin. ×113, reduced ⅓.)

thickened or inflamed. Within the pericardial space, a friable, vascular cystic tumor was found to be densely adherent to the base of the pulmonary artery, the aorta, and the intrapericardial portion of the superior vena cava (Fig. 1). The pericardium at the base of the heart had been invaded, as well as the right atrial wall, although no tumor mass was felt within the atrium. No mediastinal nodes were involved. A biopsy was obtained, but resection was not possible. The pericardiectomy was carried out uneventfully.

The surgical specimen (UVH No. 330787) consisted of the pericardium which measured 8 cm. by 15 cm. at its greatest dimensions and from 2 mm. to 8 mm. in thickness. The cardiac surface of the pericardium was rough in many areas and contained both recent and older organizing hemorrhage.

Microscopic sections disclosed a vascular but cellular tumor which was plastered on the cardiac surface of the pericardium in some areas and infiltrated the pericardium in others. As shown in Fig. 2, the basic pattern was that of vascular channels of varying size embedded in a fairly dense cellular background. Some of the vascular channels were occluded by organizing and recent thrombus. Many channels were reduced to slit like openings by the more cellular components of the tumor. A higher power view (Fig. 3) disclosed cells with clear cytoplasm and moderately hyperchromatic nuclei with nucleoli. The cells were arranged in a pavement-like fashion in and around vascular channels. Hemosiderin-laden macrophages were scattered throughout the tumor. Islands of hematopoietic cells were seen in parts of the tumor. Mitotic figures were not seen.

The histologic appearance was that of an angiosarcoma. The invasion of the pericardium inferred a low grade malignant potential.

The patient was treated by external irradiation with Co^{60}, a total tumor dose of 5,400 roentgens delivered in 27 treatments. As chemotherapy she is receiving vincristine, 1.5 mg. per square meter not to exceed a total dose of 2 mg. given every other week, and cyclophosphamide 300 mg. per square meter given on weeks alternating with the vincristine. She has tolerated this treatment without difficulty and there has been no evidence of recurrent pericardial effusion, mediastinal mass, or metastatic disease to the lung. She has continued symptom-free for a period of ten months.

Discussion

Harvey[15] has suggested that the clinical picture of primary tumors of the heart is determined by the structures they involve. It follows that the symptom complex of angiosarcoma of the heart is uniform because of the extreme rarity of involvement of cardiac structures other than the right atrium. A single instance of left atrial involvement has been reported as an incidental *autopsy finding* in the presence of rheumatic heart disease and mitral ste-



Fig. 3. Photomicrograph of tumor showing large cells with abundant pale cytoplasm in association with vascular channels. (Hematoxylin and eosin. ×550; reduced ⅓.)

noma.[16] Rare cases of primary pericardial or primary right ventricular angiosarcomas have been documented.[14] While many reported cases were found at autopsy to have significant pericardial effusion, most presented the classical picture of obstruction to venous return and low cardiac output; the rather benign picture of recurrent effusion presented by our patient is unusual.

Although metastatic lesions have been found in 75 per cent of the cases,[7] death has almost always been from low cardiac output secondary to obstruction at the right atrial level. The tumor pathologically is of low grade malignancy and in some cases metastatic lesions may be mistaken for benign hemangiomas because of their high degree of differentiation.[13,19]

Histologically similar tumors arising in other sites have been treated successfully by radical surgery, irradiation, chemotherapy, or combinations of these.[21,22] The only previously treated angiosarcoma of the heart responded partially to Co^{60} and cyclophosphamide.[11] When the patient died of metastatic disease, the primary tumor was smaller than at the time of diagnosis.

Our patient has been treated with cyclophosphamide and vincristine in alternating week dosage because of the demonstrated effectiveness of this combination in undifferentiated or sarcomatous neoplasms.[23] The Co^{60} has proven effective in noncardiac tumors of this type and was well tolerated by our patient. There has been no evidence of progression of the tumor and the pericardial effusion has not recurred. The chemotherapeutic agents have been tolerated without signs of major toxicity.

Since the majority of primary angiosarcomas of the heart do present a characteristic picture, it is hoped that more cases will be detected and appropriate therapy started before the patient reaches a terminal state.

Summary

Angiosarcomas of the heart, because of their almost constant involvement of the right atrium, present a unique clinical picture. This is characterized by chest pain, obstruction to filling of the right side of the heart, pericardial effusion, cardiomegaly, dyspnea, and hepatomegaly. Up to now a total of 47 patients, including the present case, have been reported, but only 6 other cases have been diagnosed ante mortem. This case is unusual in that recurrent pericardial effusion was the dominant clinical feature and the diagnosis was made at thoracotomy before the typical symptoms appeared.

Radiation therapy and appropriate chemotherapy for this patient are outlined and she currently is doing well without evidence of progression of the primary tumor or metastatic disease after a follow-up of ten months.

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Clinical pathologic conference

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Michael Geraghty, M.D.
Frank I. Marcus, M.D.
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Clinical abstract

V. O. C., a 41-year-old Negro cook, was admitted to the District of Columbia General Hospital for the first time on Jan. 7, 1968, complaining of weakness. She had been in good health until six weeks earlier when she developed a sore throat. She was again asymptomatic for the next three weeks. Thereafter she noted the insidious onset of fatigue, weakness, and general malaise which was accompanied by swelling and tenderness of her left knee. Subsequently dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea developed. The patient visited a private physician who found bilateral basilar râles and ankle edema. During the next week she was treated by mercurial injection, parenteral corticosteroids, digitalis, thiazides, expectorants, and tetracycline. Despite some subjective improvement she continued to have paroxysmal nocturnal dyspnea, weakness, and edema of the hands and ankles.

On admission she was found to be well developed, moderately obese, apprehensive, pale, and sweating. The pulse was 80 beats per minute, blood pressure measured 170/80 mm. Hg, respirations were 24 per minute, rectal temperature was 99° F. The breath sounds were decreased in the bases of both lungs. The heart sounds were somewhat distant. There were no audible precordial murmurs, gallops, or rubs. There was no evidence of hepatomegaly or splenomegaly. Minimal pitting edema was present in the lower extremities. The joints appeared normal. The hematocrit was 32 per cent, white blood cell count was 12,300 per cubic millimeter, 70 per cent of which were polymorphonuclear cells. The urine had a specific gravity of 1.010, was free of glucose, acetone, erythrocytes, and casts, contained 2+ protein (later only trace) and 2 to 4 leukocytes per high power field of sediment. The blood urea nitrogen was 38, creatinine 2.3, total bilirubin 4.3 with direct reacting 2.3, and glucose 225 mg. per cent. The serum sodium was 130, potassium 4.2, chloride 88, and carbon dioxide 25 mEq. per liter. The total protein was 7.4 with albumin 4.5 Gm. per cent. Serum protein electrophoresis revealed a discrete increase in the alpha-2 globulin fraction. Alkaline phosphatase was 30.9 King-Armstrong units. The serum glutamic oxalacetic transaminase was 170 units. The lactic dehydrogenase was 720 units. Prothrombin time was 17 seconds (control 14 seconds). The antistreptolysin-O titer was 833 Todd units. Normal flora was cultured from the throat. Bentonite flocculation, lupus erythematosus (L.E.), and antinuclear antibody preparations were negative. The peripheral venous pressure was 11 cm. of water and the sodium dehydrocholate arm-to-tongue circulation time was 11 seconds. The electrocardiogram revealed a sinus rate of 75 beats per minute. The mean QRS axis, the QRS duration, the P-R interval, and the Q-T interval were normal. There was T-wave inversion in Leads aVF and V through V. Chest roentgenogram on admission showed "blunting" of the costophrenic angles bilaterally but no parenchymal infiltrates. There was no cardiomegaly.

On the second hospital day the patient developed migratory polyarthritis involving the ankles, knees, wrists, metatarsal phalangeal, and the interphalangeal joints. Even though aspirin therapy brought prompt relief to the joint symptoms, she developed spiking fever to 103° and progressive deterioration with delirium. On the third hospital day a ventricular diastolic gallop was heard along with alternation of the intensity of the cardiac sounds. Pulsus alternans was demonstrated (Fig. 1).

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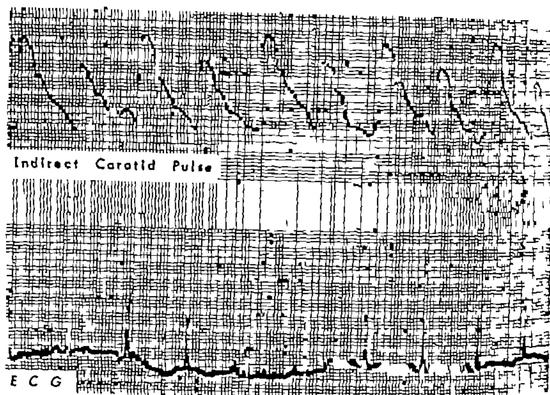


Fig 1 Indirect carotid pulse tracing showing pulsus alternans with reference Lead II electrocardiogram

At no time was a precordial m rmur heard Prednisolone, 100 mg per 24 hours, was started on the sixth hospital day On the seventh hospital day she was semicomatose Determinations on blood drawn at this time showed blood urea nitrogen of 143 and glucose 1,320 mg per cent. The serum sodium was 160, chloride 114 potassium 5.3 and carbon dioxide 13 mEq per liter The serum osmolality was 445 milliosmoles per liter Serum and urine acetone determinations were negative Despite intensive therapy with fluids electrolytes, and insulin, she died on the eighth hospital day

Discussion

DR. MARCUS This 41 year-old woman dated the onset of her illness to six weeks before admission when she had pharyngitis. There was an interval of three weeks when she felt well only to be followed by a severe, unremitting illness ending in death three weeks later The terminal illness was characterized by involvement of multiple organs including the liver joints, heart kidneys, and central nervous system. The antistreptolysin-O (ASO) titer of 833 Todd units was definitely elevated At this age this value should not be greater than 100 to 150 units.[1] Since the ASO titer began to rise within a week after a streptococcal infection and reached a peak within 3 to 5 weeks[2] the titer found in this patient was consistent with a streptococcal pharyngitis six weeks previously It is not clear however whether the pharyngitis was at all related to subsequent events. There is laboratory evidence documenting impairment of hepatic and renal function. The arthritis was consistent with that found in acute rheumatic fever because of its migratory nature and prompt response to salicylates. The symptoms of orthopnea, paroxysmal nocturnal dyspnea, and edema suggest left ventricular failure. However on admission gallop rhythm was not heard nor was the venous pressure or circulation time elevated. Nevertheless, when she was seen by a cardiologist (Dr Gordon A. Ewy) on the third hospital day heart failure was documented by the presence of ventricular diastolic gallop as well as pulsus alternans (Fig 1). The heart failure seemed to be secondary to myocardial rather than valvular dysfunction since no murmur was heard

The differential diagnosis here is extensive. The most likely cause of this patient's

illness is systemic lupus erythematosus because of the multiple-system involvement including arthritis in a 41 year-old woman. Several LE preparations, however were negative. The marked increase in the alpha 2 globulin on serum electrophoresis was suggestive of a monoclonal spike as may be found in multiple myeloma. Increases of the alpha 2 globulin however are nonspecific[3] and bone marrow aspiration did not show any abnormality Thrombotic thrombocytopenic purpura is possible but unlikely in the absence of thrombocytopenia. Several unusual infectious diseases should be considered I cannot exclude toxoplasmosis which can present in many forms including one characterized by multiple system involvement.[4] Leptospirosis is usually associated with severe headache and myalgias—symptoms not present in this patient.[5] I would be reluctant to make the diagnosis of either bacterial endocarditis or acute rheumatic carditis in the absence of an organic murmur It is conceivable that she could have had a combination of both acute poststreptococcal glomerulonephritis and rheumatic carditis. My final diagnosis, however would be *lupus erythematosus*

During the last two days of life she developed coma and hyperglycemia without acetonemia. This combination has been characterized as hyperosmolar coma and will be discussed by Dr Myron Lotz.

DR. LOTZ On the final day of life the patient became progressively obtunded and was found to have marked hyperglycemia and hyperosmolarity in the absence of ketosis. By definition she had the *syndrome of hyperglycemia, hyperosmolar nonketotic coma* of which some 130 cases have been described since the original report by Sament and Schwartz in 1957 Other features usually present are dehydration hypernatremia, and azotemia Acidosis, when present, is usually mild The mortality rate in these patients approaches 60 to 70 per cent, a fate unfortunately shared by our patient despite vigorous therapy with hypotonic fluids insulin and potassium.[7]

This syndrome may occur in the following settings (1) during convalescence from burns when on a high carbohydrate diet (2) during peritoneal dialysis and hemodialysis[8] (3) during therapy with thiazide diuretics (4) during both long and short term corticosteroid therapy[7] (5) during nonspecific stress i.e infections, trauma and (6) without known precipitating cause.

Patients with this syndrome generally have the following characteristics (1) They are usually elderly but the syndrome has been reported in patients of 18 months[11] and 16 years of age[12] (2) they may or may not be known diabetics and following recovery some patients remain diabetic while others regain normal glucose tolerance[7] (3) upon recovery the diabetes, when present is usually easily controlled with small doses of insulin and (4) with one exception, a 24-year-old woman with ketosis-prone juvenile diabetes whom we saw recently the syndrome has not occurred in a ketosis-prone individual.

The syndrome has been reported[12-14] in seven patients receiving corticosteroid therapy The mechanism by which corticosteroids precipitate this syndrome is unknown Corticosteroids facilitate gluconeogenesis, impair sensitivity of peripheral tissue to insulin and are antiketotic. Although diabetes develops in 5 to 7 per cent of patients on corticosteroids it is usually mild To my knowledge, no patient with this syndrome has had evidence of adrenal hyperfunction. The pathogenesis of hyperglycemia and the reason for the absence of ketosis is unclear

Therapy for this syndrome includes fluids, preferably hypotonic, either intravenously or by gastric tube potassium and insulin The insulin requirement is usually about 200 to 300 units but can vary enormously some patients have required more than 13 000 units, while one patient recovered without any insulin.[14] The high mortality (60 to 70 per cent) has been attributed to rupture of cerebral veins resulting from the hyperosmolarity At necropsy pathological findings are usually minimal and nonspecific.

There remains a great deal to learn about the pathogenesis and therapy of this entity which seems to have been the major cause of death in this patient.

Dr William C. Roberts will discuss the pathologic findings.

DR. ROBERTS From the numerous abnormal clinical and laboratory findings,

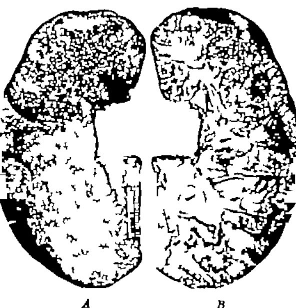


Fig 2 Kidney It is of normal size and the external surface is smooth (A) The discoloration of both external and t (B) surfaces resulted from severe congestion of the renal vessels. The parenchyma was norm l hist logically



Fig 3 Pericardium. (A) Anterior surface of the heart showing diffuse pericardial disease. The visceral and parietal pericardia were adherent to one another (B) Section of right trium showing obliteration of the pericardial space (Hematoxylin and eosin stain ×25)

multiple organ systems appear to have been involved including kidneys, heart, liver and blood Terminally the blood urea nitrogen was 143 mg per cent, and the specific gravity of the urine was never over 1 012. The kidneys were of normal size, their surfaces smooth but each was severely congested (Fig 2) Histologic examination of the kidneys disclosed no abnormalities other than congestion. Thus, the azotemia was prerenal

The cardiac necropsy findings are especially interesting in view of the absence of precordial murmur and friction rub. The parietal pericardium was firmly adherent to the visceral pericardium by fibrofibrinous adhesions (Fig 3). Thus, diffuse pericarditis, which had obliterated the pericardial space, was present. Histologic examination of the pericardium disclosed inflammatory cells, consisting mostly of mononuclear cells, but occasionally a few polymorphonuclear leukocytes, in addition to fibrin and fibrous tissue. The heart weighed 400 grams. The mitral valve leaflets were diffusely thickened but the chordae tendineae were probably normal (Fig 4) Thus, the mitral valve was anatomically abnormal yet functionally normal Grossly the left atrial endocardium and atrial and ventricular myocardium appeared normal. The aortic valve cusps were slightly but diffusely thickened. In addition, a small verruca was present on the ventricular aspect of each of the three aortic valve cusps (Fig 4) Verrucae were located at the points of contact of the cusps during ventricular diastole. Histologic study of the verrucae disclosed that they consisted primarily of fibrin, but numerous inflammatory cells were present in the aortic cusps adjacent to, as well as at a distance from the verrucae (Fig. 5) No organisms were present in the verrucae (Brown and Brenn and periodic acid-Schiff stains) A large number of inflammatory cells, mainly mononuclear but a few polymorphonuclear cells, were present throughout the entire aortic valve cusps. In addition the cusps were edematous and contained numerous vascular channels. Similar inflammatory cells were present in the mitral and tricuspid valve leaflets (Fig 5)

The specific diagnosis in this patient was

obtainable by examination of histologic sections of myocardium. All sections of myocardium disclosed Aschoff bodies (Fig 6) Thus, this patient had *acute rheumatic fever* The myocardial fibers appeared hypertrophied and focally degenerated In addition to foci of mononuclear cells in the myocardium there were also foci consisting mainly of polymorphonuclear leukocytes. Thus, the myocarditis was acute as well as chronic. The inflammation was seen in the walls of all four cardiac chambers, but primarily in the ventricular myocardium. A few foci of replacement fibrosis, often adjacent to Aschoff bodies, were present in sections of the myocardial wall (Fig 6) The coronary arteries were normal.

Elevation of the blood sugar and total



Fig 4 Interior of the left side of the heart. (A) Opened aorta, aortic valve and left ventricle. A small verruca (arrow) is present on each of the three aortic valve cusps which are mildly but diffusely thickened (B) Opened left atrium, mitral valve, and left ventricle. Both mitral leaflets are diffusely thickened, and the ventricular wall is mildly thickened.



Fig. 5 Portions of aortic and tricuspid valvular leaflets. (A) Verruca on aortic valvular cusp (B) Section through tricuspid valve leaflet. Grossly this valve appeared normal, but histologically it was edematous and contained many acute and chronic inflammatory cells. (C) A close-up of the polymorphonuclear leukocytes in the brackets is shown in the photomicrograph. (Hematoxylin and eosin stains on each (A) ×81 (B) ×160, (C) ×628)

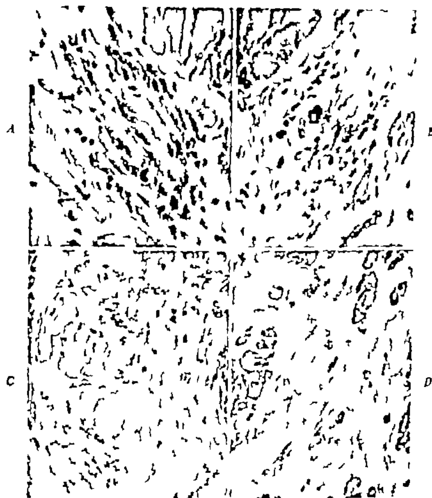


Fig 6 Myocardium (*A*) and (*B*) Aschoff bodies in left ventricular walls. (*C*) Extensive inflammation including one Aschoff body in another area of left ventricle. (*D*) Scarring of left ventricular wall apparently the result of healing of the inflammatory process. A single healing Aschoff body is present.

bilirubin levels in this patient requires explanation. Sections of the liver showed centrolobular hemorrhage and degeneration of mild to moderate severity The cause of these changes is uncertain but acute hepatic arterial hypoxia is a possible explanation. It is well appreciated that central venous congestion may be the cause of centrolobular hepatic hemorrhage and necrosis but these changes may also result from arterial hypoxia of the liver Ligation of the hepatic artery probably produces the same anatomic lesion as occurs after ligation of the hepatic vein just as it enters the vena cava. However the presence of hyperglycemia raises doubts regarding the possibility of hepatic arterial hypoxia causing the changes in the liver There is suggestive evidence that hypoglycemia not hyperglycemia is a consequence of hepatic hypoxia.[11] Prolonged hepatic ischemia may have caused the hyperbilirubinemia.

The bone marrow was extremely hypercellular but the increase in cells appeared to have been the result of an increase in all three blood elements. The brain was grossly edematous and histologic sections did not show any abnormality

In summary this patient had acute *rheumatic fever* with *pancarditis* (pericarditis, myocarditis and endocarditis). The disease in this patient was unusual in the following respects (1) the patient was 41 years of age when the initial clinical attack of acute rheumatic fever occurred. (2) the course of the illness was fulminant since she had been well seven weeks before

death (3) despite gross anatomic involvement of two cardiac valves and histologic involvement of three, no precordial murmur was heard (4) although there was extensive pericarditis, a precordial friction rub was not heard and (5) the severe functional impairment of the kidneys and liver was apparently secondary to severely decreased cardiac output which in turn was the result of the rheumatic myocarditis.

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Fundamentals of clinical cardiology

Respiratory and cardiac effects on venous return

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Cardiac output is influenced by a variety of controlling mechanisms. However, it is self-evident that the heart can pump only the blood it receives. Although minor discrepancies may exist from beat to beat, the average volume of venous return determines the cardiac output. Venous return itself is controlled by complex mechanisms including, among others, venous tone, heterometric autoregulation, transmitted arterial pressure, tissue pressure, and feedback control systems. The factors lying distal to the capillary are nevertheless of fundamental and quantitative importance in affecting venous return and therefore cardiac output.

This study will review two of the prominent factors that alter venous return: respiratory activity and the direct *vis a fronte*† influences of cardiac action itself. Both respiratory and cardiac activity will be presented in terms of their influence on normal venous flow in the thoracic inferior and superior venae cavae. In addition, alterations in normal venous return produced by anesthesia, positive pressure ventilation, thoracotomy, and changes in posture will be described. The dog was the experimental animal used in the studies to be presented.

Normal flow patterns

Several authors[1-4] have described the pulsatile pattern of thoracic vena caval flow. Although this pattern is due to several factors, respiratory effects predominate in the closed-chest normal animal. These effects result in a large increase in flow during inspiration, with return to a fairly constant flow level during expiration. As might be expected, the variations due to respiration are usually more pronounced in the inferior thoracic vena cava than in the superior cava, partially due to the combined effect of the pumping action of the abdominal and thoracic musculature on inferior caval flow and probably also, in part, due to a greater tendency for the superior caval veins to collapse during inspiration. The latter occurs more readily at the point where the great veins enter the thorax. If, however, the negative pressure in the thorax is removed by opening the chest cavity, the positive abdominal pressure still rhythmically influences inferior caval

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†Force from in front.

flow whereas superior caval flow becomes independent of respiration.[1] Some authors have also postulated that the descent of the diaphragm may partially compress hepatic and portal veins, although the intrahepatic veins resist collapse. This mechanism however has not been clearly demonstrated in the unanesthetized animal

Superimposed on the variations in central venous flow due to respiration are the effects of cardiac activity (*vis à fronte*) These may be seen more easily in the open-chest animal, but frequently can also be clearly discerned in an animal with relatively slow shallow respirations. The alterations produced consist of two prominent decreases in flow associated with atrial contraction and with the mid portion of ventricular systole when atrial venous pressure is increasing (the V wave of venous pressure) The decrease in venous flow associated with atrial contraction often is so large as to result in a negative or backward flow of blood in the cavae immediately adjacent to the right atrium This regurgitant flow tends to be more prominent in the inferior than in the superior vena cava, but may be seen in both. The anatomical manner of opening of the superior cava into the right atrium may result in a more physiologically effective valve than the Eustachian valve at the entrance of the inferior cava into the atrium. If the veins are filled more completely as just after an inspiratory effort, the backward flow due to atrial contraction is more pronounced and decreases during the expiratory period

There are likewise two periods of increased forward flow associated with the cardiac cycle. These are associated primarily with the descent of the base of the heart during the early phase of rapid ejection and with the opening of the right atrioventricular valve and the rapid inflow phase of the cardiac cycle. Smaller effects are associated with the bulging of the tricuspid valve into the right atrium during isovolumetric contraction (decreased flow) and with the reduced inflow phase (nearly constant flow) Obviously therefore the

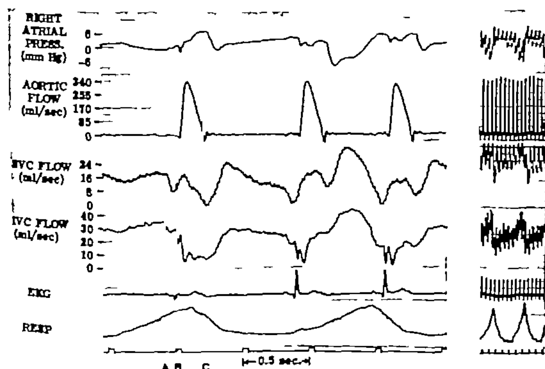


Fig 1 Pulsatile flow tracings obtained from dog ith implanted flowmeter probes on he SVC IVC nd aorta and Silastic catheter in he right trium The animal has received morphine sulf produce slower heart rate. Right panel several minutes later Time marks in seconds I spiration is an upward deflection.

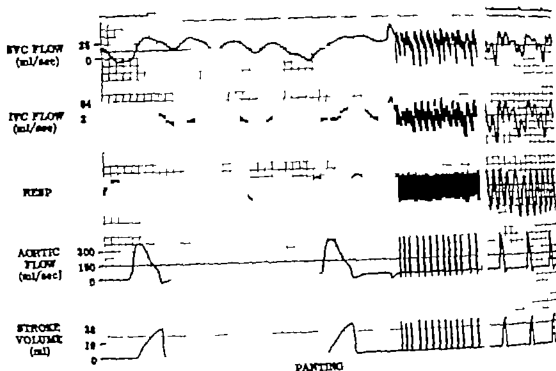


Fig. 2A. Effects of panting on flow in the unanesthetized animal. Time marks in seconds; inspiration is an upward deflection.

RESP

AORTIC FLOW (ml/sec) 300 200 100 0

STROKE VOLUME (ml) 34 17 0

IVC FLOW (ml/sec) 80 40 0

WHINE

WHINING

Fig. 2B. Effects of whining on IVC flow. The inspiratory gasps and the corresponding flow changes may be seen during prolonged whining at the right of the figure. Time marks in seconds; inspiration upward.

thoracal *vis à fronte* has both positive and negative components associated with its total effect on venous return to the right heart.

Fig. 1 illustrates the typical pulsatile flow patterns seen in the unanesthetized animal with electromagnetic flow probes chronically implanted. The variations in superior vena caval (*SVC*) and inferior vena caval (*IVC*) flow occurring during the cardiac cycle are shown. Timing may be obtained from the EKG tracing. Vertical lines show the onset of atrial systole (*A*), ventricular systole (*B*), and ventricular diastole (*C*). The alterations produced by the slower respiratory activity may be seen in the slower tracing on the right. Also shown are the decreased flows (often actually backward flows) occurring during atrial systole. The decreases are more prominent after each inspiration, presumably due to more complete atrial filling, increased atrial pressure, and an associated increase in the force of atrial contraction. The presence of more blood in the vena cava at this time may also contribute to a more circular cross-sectional area and a decrease in venous resistance.[1]

Two observations regarding the type of caval flow pattern seen in Fig. 1 are in order. The flow patterns strongly resemble inverted tracings of right atrial pressure. Although a longitudinal intravascular ΔP is not evidently an important control factor in venous flow,[4] as is the mean level of venous pressure, it is apparent that flow and right atrial pressure are being influenced by the same factors, e.g., valve closure, A-V ring movement, etc. Interestingly, the venous flow pattern, when primarily determined by cardiac activity as in this instance, also resembles coronary arterial flow tracings. Obviously this is because the timing of the events of the cardiac cycle that influence coronary flow, although in an entirely different manner, are the same for venous flow as for coronary flow. Hence, venous return and coronary flow both decrease during isovolumetric contraction and reduced ejection, both increase during early diastole.

The normal flow patterns discussed above

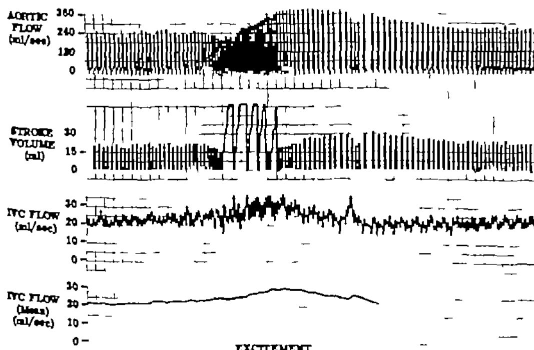


Fig. 3. Effects of excitement on IVC and aortic flows in the unanesthetized animal. Failure of the stroke volume integrator to reset properly produced the artifact seen in that tracing.

AORTIC FLOW (ml/sec) 240 120 0

STROKE VOLUME (ml) 30 15 0

SVC FLOW (ml/sec) 31 0

SVC FLOW (Mean) (ml/sec) 31 0

IVC FLOW (ml/sec) 30 20 10 0

IVC FLOW (Mean) (ml/sec) 20 10 0

STANDING | SITTING LYING | STANDING

Fig. 4-4. Transient influence of changes in posture on caval and aortic flows.

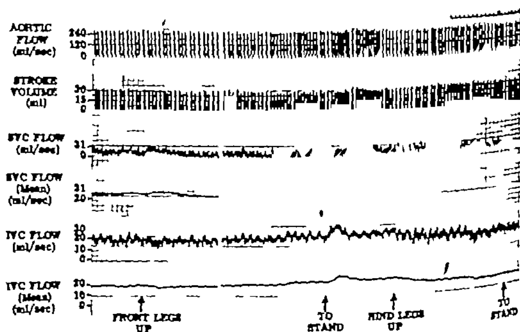


Fig. 4-B. Influence of elevating the dog's front or hind legs on caval and aortic flows. Assistant lifted hind or front legs approximately 30 degrees from horizontal, forcing animal to support himself on remaining legs.

are seen in the quiet animal lying in the prone position. Any alteration in either cardiac or respiratory activity will significantly influence the flow pattern. Fig. 2 illustrates some normal patterns which may be seen as a result of panting (*A*) and of a positive Valsalva effort (whining *B*). Similarly some effects of changes in posture and excitement are shown in Figs. 3 and 4.

Mean flows

While the above patterns of flow are important and provide a fairly accurate picture of some of the forces involved in venous return, it is the overall mean flow level that determines the amount of blood brought to the heart, and therefore cardiac output over any period of time. Estimates of the distribution of venous return between the superior cava and the inferior cava have been few. Folkow and associates[9] state that 65 per cent of the cardiac output returns via the inferior cava. In chronically implanted animals, with the azygos vein tied we have obtained mean values for inferior caval flow of 57 per cent of cardiac output in the prone animal.[19] The cardiac output in that group averaged 118 ml. per kilogram per minute. With changes in posture such as sitting, standing and 20 degree head-up and head down tilting the percentage of venous flow returning via the superior and inferior thoracic venae cavae remained essentially unchanged. Cardiac output was significantly higher only during standing but was unchanged by sitting or passive tilting, despite significant changes in stroke volume and heart rate. These data indicate that gravity plays little role in normal venous return probably due to the presence of U tubes in the circulatory system the forces cancelling in such a system. Other factors then serve to maintain the venous return in situations such as changes in posture and passive tilting. These factors apparently maintain venous return despite rather large changes in heart rate indicating that cardiac (*vis à fronte*) factors are probably not of major importance in determining overall mean flow levels. When the abdominal

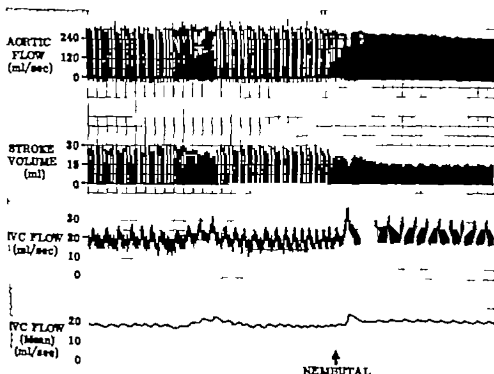


Fig. 5. Immediate effect of intravenous injection of an anesthetizing dose of sodium pentobarbital (Nembutal) (15 mg. per kilogram). Animal premedicated with droperidol-fentanyl citrate (0.13 ml. per kilogram).

thoracic pump was altered however by means of a positive pressure ventilator (see below) *an immediate alteration in* venous flow occurred indicating the relative importance of this mechanism

Effects of anesthesia

When the dog is given sodium pentobarbital there is an immediate increase in heart rate and decrease in stroke volume. Although the changes in cardiac output are not consistent there is probably a significant decrease [11,13]

Fig 5 shows a typical response to the injection of sodium pentobarbital There is an immediate increase in heart rate and decrease in stroke volume. IVC flow increased and with a decrease or no change in overall cardiac output it now represents 69 per cent of the cardiac output instead of the 57 per cent seen *in* the normal dog [11] SVC flow has, therefore decreased. Whether this represents a decrease in muscle activity of the head and neck, a decrease in cerebral blood flow or alterations due to a change in respiratory activity e g collapse of superior caval vessels due to suction remains undetermined Although other anesthetics have been studied as to their hemodynamic effects, essentially no studies have been made of their influence on venous return

Respiration often temporarily ceases or becomes very shallow immediately after pentobarbital injection during which time cardiac effects dominate the venous flow patterns [11] Later on the respiration is deep slow and regular producing the pattern of venous flow shown in the left panel of Fig 7 *A*

Abdominal-thoracic pump

During head up tilting the role of the abdominal thoracic pump in venous return tends to be accentuated This is particularly apparent in the anesthetized animal or in the animal that has been placed under sufficient stress to develop the abdominal compression reaction—a strong contraction of the abdominal muscles during the expiratory phase of respiration [11] Fig 6,*A* shows the influence of this phenomena. A major proportion of inferior caval flow now occurs during inspiration with a pronounced decrease just after each inspira-

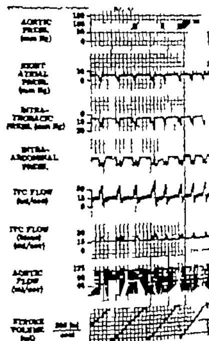


Fig 6 *A* Effects of the abdominal compress reaction on IVC flow in the anesthetized dog Intra-abdominal pressure obtained from balloon in the peritoneal cavity not calibrated.

tion The intra-abdominal pressure tracing indicates the contraction of the abdominal muscle by a rise in pressure during expiration. It has been suggested that this reaction serves to pump blood from the abdomen into the thorax[11] there is a slight but certainly not prominent increase in IVC flow accompanying this reaction. A similar reaction has not been reported in man although it may represent a variation of abdominal breathing That intermittent abdominal pressure can play a marked role in venous return is shown in Fig 6,*B* in which the abdomen was manually squeezed. Steady abdominal pressure has a similar immediate effect (Use of a bladder however was not associated with a sustained increase in venous flow levels.)

Effects of positive pressure ventilation and thoracotomy

When the anesthetized animal is ventilated by mechanical positive pressure a marked alteration in the pattern of venous return occurs, primarily in relation to the pattern due to respiratory activity Such a sequence is shown in Fig 7 *A* Inspiration no longer produces the influx of blood previously seen rather there is an actual

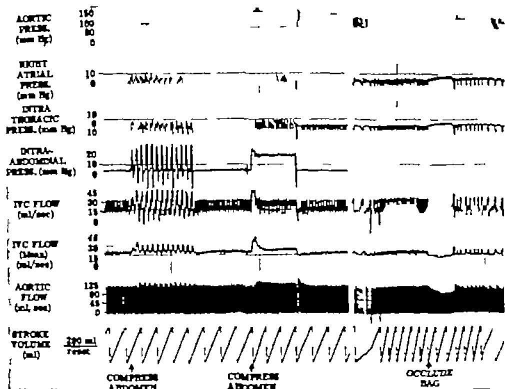


Fig 6 B Effects of manually compressing the abdomen, intermittently and sustained, on IVC and aortic flow Bag attached to endotracheal tube was occluded, raising intrathoracic pressure, in right panel

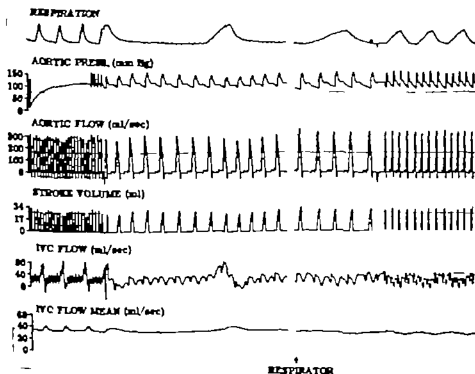


Fig 7 A Effects of attaching endotracheal tube of spontaneously respiring animal to positive pressure ventilator Inspiration is an upward deflection in the pneumograph tracing (From Abel and Waldhausen J Appl Physiol 25:479 1968)

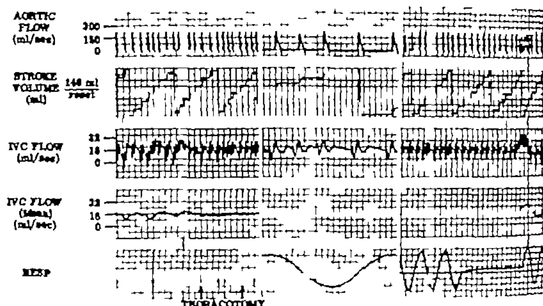


Fig 7 B Left panel Effects of acute bilateral thoracotomy on IVC and aortic flows. Middle panel: [illegible] attached to positive pressure ventilator. Inspiration is an upward deflection. Right panel: Ventilator turned off; inspiratory and vasomotor effort occurred just before ventilator was restarted.

decrease in thoracic venous flow accompanying the positive pressure produced by the ventilator. Flow then returns to a stable level during expiration. Superimposed are the cardiac effects as previously described.

As might be expected, this decrease or reversal of the normal abdominal thoracic pump pressure gradient results in a decrease in cardiac output; this amounts to about 13 per cent with even fairly minimal lung volumes.[1] IVC and SVC flow in this situation decreased proportionately.

At present there is little quantitative information relating the magnitude of the alteration in intrathoracic pressure with cardiac output and venous return. Preliminary studies[13] suggest a linear relationship between the decrease in cardiac output and the increase in intrathoracic pressure. This would be expected, of course, only if the veins involved are operating at nearly constant cross-sectional dimensions, as the changes in resistance associated with a change in diameter or shape in the veins might well be greater than that associated with the changes in pressure gradients.[2] Increasing the intrathoracic pressure, however, by occlusion of the ventilation bag results in an immediate decrease in venous flow and cardiac output (Fig 6 *B*).

Thoracotomy removes the positive intrathoracic pressure while retaining the effects of abdominal pressure (Fig. 7 *B*). The influence of ventilation should no longer be seen on the venous flows, unless the animal is spontaneously respiring, in which case abdominal respiration *will still* influence IVC flow.[1] We have *not*, however, found any appreciable immediate alteration in cardiac output or IVC flow as a result of acutely opening the chest (versus the continuously ventilated animal).[11]

Summary

Cardiac activity and respiration markedly alter the venous flow patterns in the major thoracic systemic veins. Cardiac activity (*vis à fronte*) is associated with two periods of increased and two periods of decreased venous flow corresponding to changes in atrial pressure. Respiratory activity predominates in most instances, however, producing a large increase in venous return during inspiration. Alterations in respiratory activity produced by procedures such as positive pressure ventilation, airway occlusion, whining, etc., cause much greater changes *in venous return* and cardiac output than *do changes in* posture or passive tilting. Excitement, [illegible]

and pentobarbital anesthesia can produce marked changes in venous return. Pentobarbital can increase the percentage of blood returning to the right heart via the inferior vena cava. Gravity apparently is relatively unimportant in returning blood to the heart.

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff Alan F Lyon and Julian Frieden

Phentolamine

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Phentolamine has primarily been used in a screening test for the detection of pheochromocytoma. Recent work, however has demonstrated that the drug has far greater clinical applications.

Pharmacological actions

Phentolamine is known to be an α-adrenergic blocking agent. This is based on the observation that it can antagonize or even reverse the pressor response to epinephrine the blockade thus produced is relatively transient. A mild sympatholytic action becomes manifest only with the use of very large amounts of this agent The drug also has a marked peripheral vasodilatory effect which is not blocked by atropine The drug's relatively weak sympathetic blocking action as well as its antagonism to the circulatory catecholamines cannot adequately explain the striking vasodilation that results from its use under normal resting conditions. Its recently described β-adrenergic stimulating action as well as a direct relaxing effect on the vascular smooth muscle play the dominant roles in the production of this marked peripheral vasodilatation The β adrenergic stimulating action is supported by the observation that the fall in blood pressure and the increase in cardiac rate produced by 5 mg of phentolamine can be significantly blocked by the prior administration of 1 mg of propranolol Further the administration of phentolamine to rats is associated with a threefold increase in the synthesis and release of catecholamines in the heart brain, and adrenal glands. This may be a contributing factor to its β-adrenergic stimulating action

Hemodynamic actions

The administration of 5 mg of phentolamine intravenously to normal dogs each with a strain gauge arch attached to the right ventricle will increase the ventricular contractile force. This positive inotropic response in animals has also been demonstrated in humans by employing the left ventricular dp/dt This measurement is markedly increased after the administration of phentolamine The administration of this drug at an infusion rate of 0.3 mg per minute to patients in congestive heart failure produces a striking hemodynamic improvement. The cardiac output cardiac rate, systemic pressure and stroke index increase while the pulmonary artery pressure systemic peripheral resistance left ventricular end diastolic pressure and left ventricular end diastolic volume fall. Further this marked improvement of cardiac dynamics occurs within minutes, and is not associated with any untoward side effects The administration of phentolamine at a rate of 2 mg per minute produces as

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increase in the cardiac output and cardiac rate and a fall in the systemic arterial pressure. The low dose of phentolamine (0.3 mg per minute) produces a rise in the systemic pressure due to the predominant inotropic effect. The higher dose (2 mg per minute) probably produces predominant vasodilatation with a resultant fall in the systemic pressure masking the inotropic effect of the drug

Pulmonary edema

Phentolamine was also administered to a small group of patients who had spontaneous pulmonary edema. The drug was infused at a rate of 0.3 mg per minute for an average duration of 30 minutes. Rotating tourniquets were not used during the infusion of the drug and no patient was treated with additional digitalis or morphine at the time of the infusion All of the patients demonstrated with treatment, a moderate decline in the arterial pressure and prompt clinical improvement This was presumably associated with a fall in the pulmonary artery pressure and an increase in the cardiac output. A reduction in the peripheral resistance, with decreased systolic load on the heart as well as an increase in left ventricular contractility were believed to be the factors that produced the improvement in these patients. A larger series of patients should be studied to support these preliminary observations.

Use in *arrhythmias*

In experimental work on dogs, phentolamine administration can prevent nicotine sulfate- and epinephrine induced arrhythmias and convert metacholine-induced atrial flutter fibrillation and atrioventricular nodal rhythm to normal sinus rhythm. Phentolamine administration can also prevent the appearance of pronounced bradycardia during electrical stimulation of the vagus nerve

In an additional study ten normal dogs were acutely digitalized with ouabain until electrocardiographic abnormal ties of rhythm appeared Phentolamine infused at 0.3 mg per minute rapidly abolished ventricular tachycardia in 4 of 5 cases, ventricular premature contractions in 3 cases, complete heart block in 1 case, and increased the rate in 1 case of sinus bradycardia.

In man, the experience with phentolamine in diminishing or abolishing ventricular premature contractions has been very encouraging When the drug is infused at 0.3 mg per minute, this favorable effect is seen in digitalis as well as in nondigitalis-induced ventricular premature contractions. The mechanism of phentolamine's antiarrhythmic action is not fully understood

Use in shock

Phentolamine has been administered at 0.6 mg per minute to patients in shock. Clinical improvement was manifested by a reduction in mean circulation time, an increase in peripheral skin temperature, and an increase in urine flow However the decline in the mean arterial pressure in spite of an increase in the cardiac output, limited the drug's clinical applicability If one administers 0.3 mg per minute of phentolamine to such patients, one might expect an increase rather than a fall, in the systemic pressure. This hypothesis has been tested in 8 dogs in hemorrhagic shock. Phentolamine infused at 0.3 mg per minute produced a rise in the mean femoral artery pressure as well as an increase in the cardiac output. Further studies are required to evaluate the drug's usefulness in this condition.

Use as a bronchodilator

Phentolamine has an antispasmodic action in the isolated guinea pig lung The administration of phentolamine in a dose of 10 mg per kilogram exerts a prophylactic action in cases of experimental histaminic and allergic bronchial asthma in the guinea pig as well as a curative action in the case of histaminic bronchial asthma.

One study has shown a significant improvement in pulmonary function tests in normal man as well as in patients with pulmonary emphysema when a nebulizer containing 5 mg of phentolamine in 1 c.c. of water was used Further a comparable degree of improvement was observed in the same subjects when a nebulizer containing isoproterenol was used In view of the results of this study continued

investigation of phentolamine as a bronchodilator is warranted

Summary

Phentolamine is very similar to isoproterenol in its mode of action. Both of these drugs can increase the ejection of blood from the heart. This is the result of positive inotropism and a reduction in afterload to contraction. The latter occurs *through primary vasodilatation and* ease of runoff of blood during systole. However phentolamine, unlike isoproterenol does not produce an alarming *tachycardia nor* a disturbing arrhythmia. Further investigation of phentolamine is warranted in view of its recently discovered properties.

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Annotations

Paralysis of the facial nerve and congenital heart defects

In December 1967 and again in December 1968 Cayler[1,2] described the association of unilateral paralysis of the lower lip depressors (the mentalis and the quadratus labii inferior) and congenital heart defects in a total of 14 infants. Marino[3] had previously described the isolated neurologic component of the syndrome and suggested possible etiologies. Twelve of Dr. Cayler's 14 cases had ventricular septal defects, often associated with other cardiac and extracardiac lesions. He offered as possibilities the close spatial relationship of the developing hyoid arch to the cardiac primordium and/or the temporal relationship of the facial innervation to cardiac septation. A subclinical viral infection during the fifth week of gestation could be the cause for the combination of abnormalities.

During the past year we have seen three cases with this association of defects. The data is presented in Table I in a manner similar to the previously reported cases.

The duration of the seventh nerve paresis in Cayler's cases is not presented. Two of the present cases were transient, disappearing by the age of four months. The significance of this relates to the eti-

Table I Clinical data

Patient	Birth date	Cardiac lesion	Facial paresis	Birth history			Maternal history			Comment
				Gestation (weeks)	Birth wt. (grams)	Forceps	Age	G/P†	Presentation	
C. G.	3/15/68	Severe pulmonary stenosis with intact ventricular septum and right to left shunt at P.F.O.*	Left (transient)	40	3,400	No	25	3/2	Double footling	Mother took thyroid medication for obesity
S. Mc.	7/14/68	Truncus arteriosus, probable Type II, unusual ventricular position	Left	39	3,100	Yes	4	2/2	Vertex	Infant has mild left sided paresis, minor left motor seizures, facial dysmorphism with low set ears; bilateral inguinal hernias
V. D.	3/20/68	Pulmonary atresia with hypoplastic right ventricle and intact ventricular septum	Right (transient)	40	3,660	No	19	1/1	Vertex LOA‡	Infant born with asymmetry of head and face, most marked on left

*P.F.O. Patent foramen ovale.
†Gravida/Para.
‡Left occipito-anterior.

ology of the lesion and suggests either trauma or infection, both of which are likely to subside. Hoefnagel and Penry presented six cases of seventh nerve paresis three of which spontaneously improved. Patient S. Mc., whose facial nerve paresis has persisted, has associated left mild hemiparesis and minor motor seizures. This suggests a more central etiology of his neurologic lesion.

The purpose of this communication is not only to corroborate the findings of Dr. Cayler but to caution against the assigning of a single etiology to this combination of lesions.

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Growth hormone levels in children with congenital heart disease

The association of congenital heart disease (CHD) and decreased linear growth is well known,[2] but a causal relationship has not yet been established. Linde and associates[4] observed the greatest retardation in patients with cyanotic CHD, but height could not be further correlated with the degree of cyanosis. He explored several possible etiologies, but concluded that neither tissue anoxia, infection, pulmonary hypertension, nor poor nutrition were responsible for the impaired growth in CHD.

The possibility that children with short stature and CHD have decreased levels of serum human growth hormone (HGH) has not been previously investigated. Conceivably, impaired circulation in the area of the pituitary gland secondary to CHD might result in diminished pituitary acidophilic function.

Subjects for the present study were 107 patients (57 males and 50 females, aged 2 to 18 years) with CHD being followed by the Pediatric Cardiology Section, University of Michigan Medical Center. Diagnoses varied, but all children were inpatients admitted for cardiac catheterization. They were classified according to height, and by the presence or absence of cyanosis. Fasting serum samples for HGH assay were obtained the day of, but prior to, catheterization. HGH determinations were performed by a radioimmunoassay method previously described in detail.

Seventy-three patients with heights below the fiftieth percentile[4] had a mean HGH level of 8.5 mμg per milliliter with a median value of 5.6; the 34 children with heights above the fiftieth percentile had a mean HGH of 6.1 and median of 3.9. Of the subjects in the shortest group, 34 were below the tenth percentile in height; mean and median HGH levels for these children were 6.5 and 4.1, respectively.

Thirteen of the patients were cyanotic and had mean and median HGH levels of 8.3 and 4.8 mμg per milliliter. The remaining children with noncyanotic CHD had mean and median values of 7.6 and [illegible], respectively.

Calculation of standard deviations was not appropriate because the data tended to be skewed to the right. However, nonparametric analysis using chi-square revealed no significant difference between the HGH medians of any of the groups when divided by height or by presence or absence of cyanosis.

This study again confirms the association of CHD and impaired growth. 68 per cent of the patients were below the fiftieth percentile for height, and 32 per cent were below the tenth percentile. However, there was no positive correlation between height and fasting HGH. It is possible that some patient may have shown a diminished HGH response if the insulin or arginine provocative test had been performed. On the other hand, it has been suggested that a fasting HGH level of 6.0 mμg per milliliter or more is probably indicative of normal growth hormone responsiveness even in the absence of further studies. Forty-nine per cent of the patients with heights below the fiftieth percentile fell into this category compared to 55 per cent of the larger children. Thus, it seems likely that the same conclusion might have been reached had more elaborate studies been performed. Finally, the few children with cyanotic CHD had HGH levels comparable to the acyanotic group, suggesting that HGH production may be relatively indifferent to decreased oxygen saturation of the blood.

I summary fasting HGH levels in a large group of children with CHD did not appear to correlate with height percentile. Whatever mechanism may be responsible for the decreased growth of patients with CHD is not manifested by diminished levels of HGH in the fasting state.

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Hemodynamic alterations produced by prolonged urethane anesthesia in the intact dog

When studying hemodynamic phenomena in anesthetized animals, the choice of the anesthetic agent is of paramount importance. The time course of hemodynamic alterations produced by the anesthetic and the metabolic effects as well as the influence on the phenomena being tested must be carefully assessed. Urethane is commonly used anesthetic in animal experiments. However little has been recorded in the literature on the hemodynamic effects of prolonged urethane anesthesia alone in intact animals. The effects become more important as experimental designs become more complex. Thus, studies were conducted by us to learn the hemodynamic alterations produced by prolonged urethane anesthesia in the intact dog These studies were necessary for proper evaluation and interpretation of physiologic data.

Five mongrel dogs, averaging 16.4 kilograms, were anesthetized with 1.5 to 2.0 Gm. per kilogram of urethane (ethyl carbamate) Catheters were

Table I The time course of hemodynamic phenomena in intact dogs anesthetized with urethane (average values for 5 dogs)

Time after induction of anesthesia (hr)	FA (mm. Hg)	PVS (mm Hg)	LA (mm. Hg)	PA (mm. Hg)	RA (mm. Hg)	C I (c.c./Kg)	PBV (c.c./Kg)	HR (beats/min.)	RR (breaths/min)	SV (c.c./beat)
1.0	132	—	—	—	—	190	—	136	—	22.7
1.5	130	10.7	3.6	16.7	+2.4	185	9.20	152	36	19 4
2	127	9 0	2.7	16.6	+1.2	165	8.81	158	40	18.0
2.5	124	8 6	1.5	14.9	−0.6	151	6.35	156	35	16.3
3	120	5.9	1.7	14.6	+0.2	135	10.66	153	36	14.6
3.5	115	4.5	0.7	13 4	−0 8	118	9 71	155	36	11.8
4	112	4.3	−0.2	13.0	−0.2	103	10 05	168	40	10.5
4.5	120	5.1	−1.4	12.8	−0 7	113	10.78	170	35	10.5
5	111	6.3	−0.7	12.8	−1 4	100	9 44	165	38	9.5

Abbreviations: FA, Femoral artery; PVS, small pulmonary vein; LA, left atrium PA, pulmonary artery RA, right atrium C.I., cardiac index; PBV pulmonary blood volume HR, heart rate; RR, respiratory rate SV stroke volume.

placed in the aorta, right trium pulmonary artery left atrium, and a mall left lower lobe pulmonary vein. Pres ures were recorded imultaneou ly using St tham tra sducers (P23Db) nd a Electronics for Medicine recorder. C rdiac output and pulmonary blood volume were determined by the indicator d lution technique u ing indoc ine green (Cardio-Green). Strok ol me y temic scular res tance pulmonary scular res t nce and pulmonary enous resi t nce were alculated by tandard for mula. Heart and respir t ry tes were contin uously mon t red. The rtic nd right t ial cath ters were introduced immediat l fter induction of nesthesi for immed t ndic tor dil tion tudy. Approximat l one hour w req ired t complet the prep t n f the dog f r tudy. The arious par meter were recorded over period f 5 hours.

The d ta re summarized in T ble I. The result were essentiall th same f ll dog. Cardiac out put, trok ol me nd pres ures in the femoral rtery mall pulmonary ein left trium pulmonary rtery nd right atrium declined lowly for pproximatel 3 hour. A l ght rise w then noted n these lues duri the fourth hour only t decl ne progress l thereafter nt l the nimal either died or w put t de th.

Heart t re sed th oughout the period of observation. Pulmonary blood volume declined lightly during the first 2 ½ hours after hich it returned to the in tial level where it remained f the duration of the period f observation. The respiratory rat remained unchanged.

These d t how that the changes in hemodynamic phenomena secondary to urethane occur slowly so that tudies in hich control and experiment l results are obtained within a 15 to 30 minute interval might be satisfactory hereas after 1 hour of urethane nesthesia the results ould be difficult to interpret. Studies requiring long periods of observation w th the a imal under urethane anesthesia would be almost impo ible t interpret. Furthermore, it i prob ble that some pharmacologic agents and other factors might even accelerat or at least modify the hemod namic and deleterious effects of urethane thus confusing phy iol gic observations. Fi lly the influence of urethane must be considered whenever interpreting data obtained from tudies in which urethane is sed.

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Agranulocytosis following procainamide administration

The ide effect of procainamide uch nausea, norexia, abdominal pain, pruritus, urticaria, fever nd chills re relativel common. Such m nor undesirable effect ma be justifiabl t lerated in light of t specific value in the control f rdiac ar rh thmias.

While most attention is given t the cardiac rhythmicity nd other w ll-known ide effect of procainamide onl 6 cases of gran locytos due to procainamide have been reported in the world liter ature. Tw of the 6 patient died a result of this adverse effect. In this hospital w encountered another case of granulocytosis that terminated in death following the administration f procainamide for the treatment f paroxysmal trial tachycardia. Since this serious complication ha not been well publicized, it deserves further ttention.

Case reports

T. B. a 75-year-old Caucasian male had had repeated bout of paroxysmal atrial tachycardia since 1961. Prior to his final dmission t this hospital he wa treated twice with chloramphenicol. In 1957 he received 51 Gm. of chloramphenicol in the course of 2 months for cholecystitis. I J ne 1963 the patient had a cholecystectomy. There was an erythematous eruption over his arms, secondary to antibiotic tre tment with treptomycin, Erythromycin (Coly-Mycin), and chloramphenicol. The r sh d sappeared after the drugs ere discont nued. There w one whit count f 3,900 per c mm. in 1963. All other whit blood count between 1961 and November 1967 were within normal limits.

I November 196 the patient as admitted to this V.A. hospit l for treatment of paroxysmal atrial tachycardi . On quinidine the patient experienced malaise fever chill and abdominal discomfort. Thus, he w pl ced on procainamide 500 mg. every 6 hours orally. At th t time the hemoglobin was 14.6 Gm. per cent nd the hematocrit as 41 per cent. The white blood count as 4,600 cells per mm with normal differential counts and an adequate number of platelets. His condition improved and his cardiac rhythm became normal. He was discharged in December 1967 on procainamide and digitalis. Forty-tw d ys later the patient was seen for follow-up care. He appeared to be well and the total daily dose of procainamide was decreased from 2,000 mg. to 1,500 mg. A hemogram was not obtained.

On Feb. 8 1968, he as admitted with the complaint of malaise fever chills, nausea, vomiting, and persistent oozing of a watery foul-smelling, brownish tool. These symptoms had begun approximately

8 hours prior t admission. Physical examination at the time of this admission revealed an acutely ill, elderly male. The oral temperature was 102° F the blood pressure was 170/98 mm. Hg Other pertinent findings included dry tongue, slight cardiomegaly and sinus tachycardia. A brownish, foul-smelling stool oozed from the anus.

The admitting laboratory data on February 9 1968, showed. hemoglobin 13.5 Gm. per cent hematocrit, 39 per cent white blood count of 700 cells per c. mm. with almost 100 per cent lymphocytes and no granulocytes on the smear The number of platelets was adequate A repeat hemogram on the same day confirmed essentially the above findings. Procainamide was discontinued and paroxysmal atrial tachycardia occurred shortly after admission and was terminated by vagus stim lation.

A sternal bone marrow aspiration was done on the following day and showed 1 per cent myeloblasts, 3 per cent progranulocytes, 1 per cent myelocytes, no mature granulocytes or monocytes, 29 per cent lymphocytes, 5 per cent histiocytes, 7 per cent plasma cells, 4 per cent pronormoblasts, 5 per cent basophilic normoblasts, 4 per cent polychromatic normoblasts, 41 per cent orthochromatic normoblasts, and a normal number of megakaryocytes. The pathologic diagnosis of this bone marrow picture as hypoplastic bone marrow agranulocytosis.

Pseudomonas aeruginosa was found in cultures of stool, peripheral venous blood, and bone marrow The patient was started on intravenous fluids and antibiotics. He received gram of cephalothin (Keflin), 5,000 000 U of penicillin, and 3 Gm. of chloramphenicol intravenously in the course of 2 days. Despite the massive doses of antibiotic treatment, he died 41 hours after admission. Significant autopsy findings showed diffuse theromatous plaques in the coronary arteries ithout evidence of recent occlusion or thrombosis. The liver and spleen ere both markedly enlarged due to congestion. Positive microscopic examination of the lungs confirmed the diagnosis of pulmonary edema and the congestion in the sinusoids of the liver and spleen. The bone marrow taken from the lumbar spine was hypocellular and there was a complete absence of cells of the myeloid series.

Discussion

A review of the 7 cases, including this patient, provides some definitive and possibly meaningful information (Table I). Even though procainamide was discontinued in all 7 patients, only 4 recovered from the complications of agranulocytosis by discontinuing procainamide The mean age of the 7 patients was 71.2 years, with range from 56 t 87 years. The majority of these ere males (5 out of 7). None of them developed agranulocytosis m mediately following the initiation of the procaina mide therapy The shortest period of time for the development of agranulocytosis following the drug therapy as 26 days, while the longest period of time for the appearance of the same did not exceed 78 days. The daily doses dministered to these patients ranged from 750 to 4,500 mg daily except in one case m hich the da to day dose of procaina mide was unknow the remaining 6 patients re ceived a mean total dose of 110 000 mg The lowest total ingested dose before agra ulocytosis as 36,500 mg while the highest total dose was 314,275 mg

In our case and in 2 others, similar history of previous exposure t procainamide was noted It is interesting to note that no leukocyte agglutinins and platelet agglutinins were present in the serum of the patients recovered from agranulocytosis. The fact that leukocyte agglutinins ere absent after previous exposure to procainamide, and that the white blood count remained normal during a period of eeks while receiving procainamide suggests strongly against the immunologic basis for this agranulocytes.

When adverse drug reactions develop one al ays wonder whether the particular patient is mutually hypersensitive, not necessarily t just one drug but also to other drugs. I the case of procainamide induced agranulocytosis, only 2 of the 7 reported cases had histories of previous hypersensitivity reac tions to other drugs besides procainamide In the present case our patient had previous episode of

Table I A summary of the seven cases of agranulocytosis following procainamide therapy

Author	Year	Age	Sex	Days of exposure	Daily dose (mg.)	Total dose (mg.)	Outcome
Miller Pollock, and Griffith[4]	1951	70	M	78	1 000	78 000	Death
Inouye, Millar and Townsend[2]	1951	81	F	48	750	36 500	Recovery
Austin, Dunn, and Schiller[3]	1951	71	F	77	750–4 500	Approximately 316 275	Death
Fabregoule and Messerschmidt[5]	1956	68	M	26	1 500	39 000	Recovery
Takeners and Teimon	1965	71	M	78	1 000	78 000	Recovery
Ostert[6]	1966	56	M	30	?	?	Recovery
Wang and Schuller	1968	75	M	63	750–1 000	113 500	Death

kin rash but had only one wh t blood cell cou t at 3,900 with norm l cou t preceding and after th t determinat on wh le the p tient wa recess   Large doses of ntibiotics includ ng hloramphenic l

The fundament l re son wh some drugs produc granulocytos   unknown It ha been postulated that the mecha ism for chlorpromazine- nduced ag anulocytos might be a irect t xic effect on the bone marrow   used b   nh ting DNA ynthes   However it w uld be interesting to determine whether proc in m le ha   similar toxic effect to that f chlorprom ine

The thors sh to acknowledge the pport f the Amer an C ncer So iety M l   kee W

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Letters to the editor

Dilantin in treatment and prevention of cardiac arrhythmias

T the Editor

I read with interest the article entitled "The Clinical Use of Diphenylhydantoin (Dilantin) in the Treatment and Prevention of Cardiac Arrhythmias by Helfant and associates (Am. Heart J 77:315 1969).

It should be noted that one of the ECG (Fig 1) is mounted upside down. I differ with the authors regarding the interpretation of their Fig 3 which appears to be supraventricular tachycardia with aberrant conduction rather than ventricular tachycardia.

On the whole I am in agreement with most of their conclusions, namely (1) Dilantin is more effective in treatment of ventricular than atrial arrhythmias (2) it is most effective in treating ventricular arrhythmias caused by digitalis excess; and (3) Dilantin ben given prior to DC countershock to patients receiving digitalis reduces postshock arrhythmias.

However the authors did not compare their results of use of Dilantin with those following intravenous lidocaine as they did with procaine amide. It is generally agreed that lidocaine gives better control of arrhythmias with less depression of the heart than procaine amide.

While the authors quoted the favorable experience of others on the prophylactic use of Dilantin on patients following myocardial infarction, they did not present clearcut data of their own to support their conclusion. Furthermore, the total clinical experience with the prophylactic use of Dilantin in acute myocardial infarction is rather small.

Since untoward reactions and even fatalities due to Dilantin have been reported and since intravenous lidocaine is extremely effective, very reliable, and far safer in the treatment (especially following acute myocardial infarction) of ventricular arrhythmias once they hav occurred, it is hoped that more controlled and comparative studies be done with each of these drugs before Dilantin can be considered as "safe and valuable agent in [its routine use for] prevention of cardiac arrhythmias. I still remember the days when prophylactic use of quinidine as routine in acute myocardial infarction.

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Reply

T the Editor

I wish to thank Dr Cheng for his interest and comments on our paper Dr Cheng observation concerning Fig 1 is correct.

It is true, as Dr Cheng notes, that our study did not include comparison of the effectiveness of lidocaine in the treatment of ventricular arrhythmias. *However it was not the purpose of this report to* compare the effectiveness of diphenylhydantoin and lidocaine with procaine amide. The effectiveness of lidocaine as an antiarrhythmic agent is well documented. Our observations concern 12 patients (Group 2) in whom procaine amide (up to 1 000 mg), given as the initial antiarrhythmic drug failed to control the ventricular arrhythmia. The subsequent administration of diphenylhydantoin appeared t have beneficial effect in 10 of the 12 cases.

I wish to call to Dr Cheng ttention that on p. 322 it is clearly acknowledged that t date the clinical experience with the prophylactic use of diphenylhydantoin is small.

Dr Cheng ppears to be expressing note of pessimism by his statement recalling the day when prophylactic quinidine was routine in acute myocardial infarction. It is important to note that the electrophysiologic properties of diphenylhydantoin differ from those of quinidine and procaine amide. It is precisely these differences in the electrophysiologic properties which would warrant continued investigation in the area of prophylactic treatment. Thus, I am sure that Dr Cheng will agree with our statement that more definitive work is required in the area of prophylactic use of diphenylhydantoin.

Finally it is pparent that in the bsence of an ideal antiarrhythmic, the clinician must be familiar with several modalities and drugs for the treatment of cardiac arrhythmias which occur in various clinical settings.

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Oral contraceptives and thromboembolic disease

T the Editor

I have read with interest an editorial entitled "Oral Contraceptives and Thromboembolic Disease in the American Heart Journal of February 1969 over the signature of M. P Vessey of London. In this editorial, it was stated that "The epidemiological investigations thus strongly suggest causal relationship between the use of oral contraceptives and some kinds of thromboembolic disease, but the case would be greatly strengthened if the physiological or biochemical effects of their use were shown to contribute to some part of the diseases process.

W hope that our experimental studies (*Proc. Soc Exp. Biol. Med.* 122 1192, 1966 *Am. J Physiol.* 213(4) 923 1967) provide evidence of contribution of the biochemical use of contraceptives to disease processes connected with blood coagulation, and w

Announcements

THE TENTH CONFERENCE OF THE INTERNATIONAL SOCIETY OF GEOGRAPHICAL PATHOLOGY will take place in Jerusalem, Israel, from Sept. 1 to 4, 1969. Two main topics have been selected for the Conference: (1) pulmonary emphysema, (2) the cardiomyopathies. These subjects will be discussed by pathologists, epidemiologists and clinicians from various countries. Ample time will be available for short communications on these and other subjects which have a bearing on geographical pathology.

For further information please contact Dr. I. S. Levij, General Secretary of the Conference, c/o Department of Pathology, Hebrew University Hadassah Medical School, P. O. B. 1172, Jerusalem, Israel.

NATIONAL CONFERENCE AND SCIENCE FILM EXPOSITION will be held at the Shoreham Hotel and Motor Inn, September 17 to 19, 1969 in Washington, D. C. Contact for information: C. William Hughes, Program Chairman, Motion Picture Services, The Pennsylvania State University, 112 West College Ave., State College, Pa. 16801 (telephone 814-865-7653).

A COURSE ENTITLED MODERN CONCEPTS OF RADIOLOGICAL SPECIAL PROCEDURE TECHNIQUES AND ROOM DESIGN will be given Sept. 4, 5 and 6, 1969 at the Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Mo. This course will offer up-to-date information on room design and the selection of x-ray and screen equipment necessary to perform modern radiographic special procedures. The faculty will include, among others, Kurt Amplatz, M.D., John Campbell, M.D., David O. Davis, M.D., Harry Fischer, M.D., William Hanafee, M.D., J. Ruben Koehler, M.D., Stewart Reuter, M.D., Nikolai Schad, M.D., Juan M. Taveras, M.D. and Michel Ter-Pogossian, Ph.D.

THE ASSOCIATION OF MEDICAL ILLUSTRATORS will hold its 24th annual meeting, "A conference on visual communication in medicine," in Washington, D. C., at the Washington Hilton Hotel on September 14 through 17, 1969. For additional information write: Association of Medical Illustrators '69 Meeting, P.O. Box 31507, Washington, D. C. 20012.

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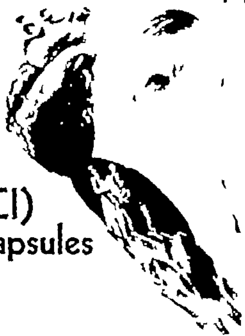
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Warnings: Caution patients about possible combined [illegible] with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Vari[illegible] effects on blood coagulation have been reported [illegible] patients receiving the drug and oral anticoagulants; [illegible]ship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may [illegible] especially in the elderly and debilitated. These are [illegible] instances by proper dosage adjustment, but are also [illegible] served at the lower dosage ranges. [illegible] have been reported. Also encountered are [illegible] tions, edema, [illegible] menstrual irregularities, nausea and [illegible] extrapyramidal symptoms, increased and decreased libido [illegible] infrequent and generally controlled with dosage reduction [illegible] EEG patterns (low-voltage fast activity) may appear during and [illegible] treatment. Blood dyscrasias (including agranulocytosis) and hepatic dysfunction have been reported occasionally [illegible] blood counts and liver function tests advisable during [illegible] therapy.

Usual Daily Dosage: Individualize for maximum beneficial [illegible] Adults: Mild and moderate anxiety and tension, [illegible] t.i.d. or q.i.d.; severe states, 20 or 25 mg t.i.d. or q.i.d. Geriatric [illegible] 5 mg b.i.d. to q.i.d. (See Precautions.)

Supplied: Librium® (chlordiazepoxide HCl) Capsules, 5 mg, [illegible] 25 mg — bottles of 50. Libritabs® (chlordiazepoxide) Tablets, 5 [illegible] mg and 25 mg — bottles of 100. With respect to clinical [illegible] sules and tablets are indistinguishable.



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Editorial

The risks of cardiac catheterization

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Cardiac catheterization, introduced to medicine first in the 1940's for cardiovascular research, has now become a standard tool for cardiac diagnosis. The basic catheterization procedure has been modified and extended to include studies with roentgenopaque contrast materials and a variety of indicator substances. There are now over 500 laboratories in the United States in which these highly specialized cardiovascular diagnostic procedures are conducted. Much of the recent progress in cardiovascular medicine and surgery can be attributed to the advances in the diagnostic techniques in these laboratories. The physician must evaluate the diagnostic value of the procedure and the risks involved before referring his patient to the cardiovascular laboratory for study. The diagnostic value of the procedures is well recognized and easily appraised, but information about the risk of complications has been more difficult to obtain.

To obtain quantitative information about the complications of cardiac catheterization, a cooperative study was organized in 1963 under the auspices of the National Heart Institute. Sixteen laboratories cooperated in this prospective study, which lasted for two years and included 12,367 procedures. Basic information was recorded on every procedure and the complications were reported in detail. The report of this study was recently published.

The 144 major complications encountered in the study were divided into the following major groups: (1) death, (2) serious arrhythmias, (3) profound hypotension, (4) complications involving the arterial system, (5) accidental perforation of the heart, (6) catheter problems, (7) serious infections, (8) serious allergic reactions, (9) embolism, (10) cardiac complications, and (11) serious bleeding. The data were also examined from the point of view of the type of study involved, e.g., coronary arteriography or transseptal catheterization.

The incidence of major complications was 3.6 per cent. Not all complications occurred in critically ill patients, as there were 23 complications in 1,112 studies in patients without organic heart disease (2.1 per cent).

The complication rate is highest in patients in the first year of life. Patients under 1 year of age constitute only 9.4 per cent of the total population under study, but 23.6 per cent of the complications occurred in this age group. The risk is lowest in the age group from 2 to 14 and remains relatively constant between 2 and 3 per cent through the upper end of the age scale.

There were 55 deaths reported in the study, yielding an overall mortality rate of 0.44 per cent, but well over half (or 38) of these deaths occurred in infants under 7 months of age. There were 29 deaths in 480 procedures in patients under months of age.

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resulting in a mortality rate for this group of 6 per cent. The vast majority of the infants dying during cardiac catheterization were found to have complex congenital malformations which would not have been amenable to surgical correction. In the age group from 2 to 59 years there were only 14 deaths in 10,004 procedures yielding a mortality rate of 0.14 per cent.

Cardiac arrhythmias are the commonest complications of cardiac catheterization but only serious potentially life threatening arrhythmias were considered to be significant. Included in this category were the following: cardiac standstill, ventricular fibrillation or prolonged ventricular tachycardia. Major arrhythmias, as defined, complicated 153 studies (1.2 per cent) and played a major role in the patient deaths in 16 patients. The most common arrhythmia was ventricular fibrillation which occurred in 59 studies (0.48 per cent). In adults, there were 23 episodes of ventricular fibrillation during coronary arteriography and 13 during other procedures. There was more than a fivefold difference in the incidence of this arrhythmia in the two sexes. The incidence of ventricular fibrillation during coronary arteriography was 1.7 per cent for females and 0.4 per cent for males. The reason for this sex difference is unknown. Six of the 23 patients who developed ventricular fibrillation during coronary arteriography were females with no organic heart disease.

It is of interest to note that in the group not associated with coronary arteriography ventricular fibrillation occurred 19 times during manipulation of the catheter in the right side of the heart as opposed to 3 times on the left side. This may be related to the increased manipulation of the catheter in the right ventricle required to catheterize the pulmonary artery rather than to a basic difference in the irritability of the two ventricles. Ventricular fibrillation reverted spontaneously to sinus rhythm in 4 patients and successful electrical defibrillation was carried out in 54. Prompt catheter withdrawal, cardiac massage and DC shock will almost always restore sinus rhythm. Only one patient, a 2 month-old infant, could not be defibrillated.

Of great practical importance is the appearance in 3 patients of severe and life-threatening arrhythmias after study had been completed and all catheters removed. In one case ventricular fibrillation occurred on the ward four hours after conclusion of the procedure. These occurrences point to the need for monitoring and close observation for several hours after the conclusion of the procedure.

Perforation of the heart or intrathoracic great vessels occurred in 100 procedures. One third of these were perforations of the right atrium in association with transseptal puncture. The right ventricle was the second most common site of perforation accounting for 21 complications. In 8 patients this chamber was perforated by a pacemaker catheter and in no instance did it result in cardiac tamponade. The aorta was punctured on 17 occasions by a transseptal needle and cardiac tamponade and death resulted in one patient. Some degree of pericardial tamponade occurred in 21 of the 100 cardiac perforations.

Arterial complications such as thrombosis, dissection, false aneurysm, and arteriovenous fistula were more common in the older age group with atherosclerosis. A wide pulse pressure, as in aortic regurgitation, interferes with the sealing of an arterial perforation and, hence, contributes to the development of arterial complications.

Pulmonary embolism and infarction occurred in 11 patients from 1 to 14 days after cardiac catheterization. Peripheral thrombophlebitis was noted in only 3 of these patients. The patient with an enlarged heart, a history of congestive failure, and a poor functional state is most prone to pulmonary embolism. Systemic embolism occurred in 17 patients and the brain was the site of lodgement of the embolus in 7.

Bacterial endocarditis was relatively rare, occurring in only 3 patients. Allergic reactions to the agents employed during the procedure were rare, occurring in only 1 patients. In only 5 could the contrast material be implicated as the offending agent.

In 10 patients, less than 0.1 per cent, was equipment failure responsible for the complication. Thus the breakage of needles or guide wires and the knotting of catheters, although dramatic and long remembered, are fortunately quite rare.

A total of 3,312 coronary arteriographic procedures were included in the study. 81

per cent of these were performed in a single laboratory There were 66 complications (1 9 per cent) including three deaths. Two of the deaths resulted from myocardial in farction and the third was attributable to asystole. Arrhythmias were the most common complication of coronary arteriography occurring in 26 procedures (0 8 per cent) Ventricular fibrillation accounted for 24 of these 26 arrhythmias and was successfully treated in all cases. Five patients experienced myocardial infarction during and immediately following the procedure

There were 1 765 transseptal left heart catheterizations in the series and complications were reported in 60 (3 4 per cent) Perforation of the heart occurred in 43 patients and was complicated by pericardial tamponade in 21 Two patients died as a consequence of cardiac tamponade.

This prospective study provides quantitative data on the risks associated with the procedures commonly performed in the cardiac catheterization laboratory The physician when referring patients to the laboratory should be aware of these risks and alert to the possible complications. The risk of complication is low (< 4 per cent) but not insignificant in the population over ? years of age and the mortality rate in this group is 0 14 per cent. Risks significantly higher than these exist in the very young and in association with the more complex procedures.

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Clinical communications

Electrocardiographic potential distributions in newborn infants from 12 hours to 8 days after birth

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Electrocardiography has greatly contributed to the diagnosis of heart diseases and their pathologic origins. Conventional electrocardiograms (ECG's) have the indispensable role of diagnosing arrhythmias and bundle branch blocks and provide essential information in the diagnosis of hypertrophy and myocardial infarction. In diseases such as myocardial infarction and ischemia, however, multiple ECG's must be taken in order to locate the abnormal sites of the cardiac muscle. Recently, Taccardi,[1] Spach and associates,[2,3] and others[4] working with adults and children investigated the potential distributions on the chest wall and demonstrated their effectiveness in giving information concerning electrical activation in the heart.

In newborn infants the ECG's are quite different from those of adults and also change with time as a result of physiologic adaptation to circumstances and hemodynamic variations. Electrocardiographic potential distributions (EPD) enable us to obtain valuable information about electrical activation in the heart of the newborn infants, although there are some serious problems (such as infants never have a share in our taking their ECG's, they are very delicate, etc.).

We have been investigating the EPD's in many clinical patients and newborn infants, and obtained important information such as local activation which could not be found by conventional electrocardiography.[5] The following is the report of the EPD's on the chest wall of newborn infants from 12 hours to 8 days after birth, which were mapped by a digital computer and line printer.

Subjects and method

Twelve newborn infants were studied. They were all delivered through the vagina and no clinical evidence of abnormality was found before or after delivery. Body weight at birth ranged from [illegible] to [illegible] kilograms. The ECG's were taken at [illegible] hours and on the first, second, fourth, sixth, and eighth days after birth in 8 babies. Four different babies were investigated every 2 days from the first day to the seventh day. The remaining 4 babies had three inspections during the first day to the eighth day. The chest ECG's were taken from 25 explored points on the anterior precordium with the limb lead as the time reference ECG while the infants were either asleep or quiet. The explored points are shown in Fig. 1. First, a square area was selected on the infant's anterior precordium. Each side of the square was equal to the distance between

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he right anterior axilla and the left one The center of the square was a point half way between the right and left papillae and was carefully fixed in case the explored points should change from day to day After the center of the square (point C3) was determined the four corner points of the square were found They are A1 A5 E1 and E5 in Fig 1 Each side of the square was equally divided into 4 sections, so that 25 cross-section points were determined with the central point being at point C3 The distance between the adjacent points was about 2 cm, although it was dependent upon the infant s size and growth About 100 pulses of ECG were taken with the limb-lead ECG from each of the 25 points.

A conductive plastic disc of 1.5 cm in diameter was used as a chest-lead electrode which was coated with silicon rubber except for a small area on one side for picking up the ECG (Fig 2) No conductive jelly was used in order to prevent skin irritation. Instead chemical filter paper of 1 cm in diameter soaked in physiologic saline was utilized for conduction between the skin and electrode The surface of the silicon rubber coating which was attached to the skin was cleaned before each measurement to avoid distortion of the electric field The ECG s taken from each explored point were recorded momentarily on a magnetic data recorder until all explored points were searched

The digital average response computer (ARC) was used for improving the simultaneity of each chest ECG which was recorded at different explored points and consequently at a different time, and for A D conversion and quantitation of the ECG Another advantage of utilization of the ARC was to reduce the noise such as variation of the ECG s base line and artifacts induced by the infant s movement Delaying of the chest ECG s was required in order to investigate the potential distributions before the trigger of the ARC since the trigger pulses were generated at the R wave of the time reference ECG The magnetic tape recorder and an acoustic delay device were utilized to achieve a delay which enabled us to investigate the potential distributions during complete ventricular and atrial

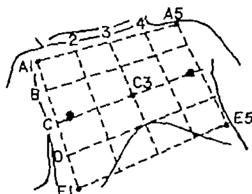


Fig 1 The sites of the 25 explored points on the chest wall.

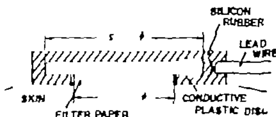
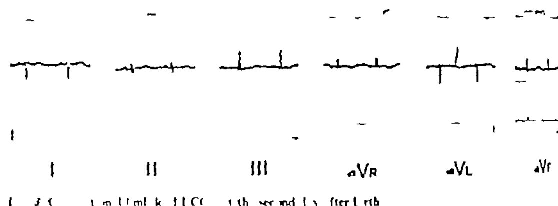


Fig 2 The schema of the chest-lead electrode

activation. Through the use of the ARC 20 pulses of the ECG with a fairly constant heart rate were added and averaged to avoid noise and also improve the simultaneity At the same time, the ECG s were converted from analogue to digital and quantitated The sampling rate of the ECG was every 2 msec. from the onset of the P wave to the end of the T wave. Using the interporation method along with the digital computer and line printer maps of the potential distributions were completed Each equipotential line printed by the line printer was equivalent to an arithmetic number or letter in the English alphabet. The maps drawn by a line printer were widened horizontally to some extent so that the potential distributions on the anterior precordium were shown on the rectangle. The right side of each map corresponded to the left anterior axilla and the left side the right one

Results

The EPD s during atrial activation and ventricular activation were investigated



F 3 C t m l l ml k 1 I C C t th second l y fter l rth

The EPD [illegible] were also mapped in order to study the daily changes. One series of the EPD during the QRS complex included 30 maps with the interval of 2 msec. Sampling time was shown by dotting on the reference ECG under the EPD.

Arithmetic number 0 meant the Wilson central voltage and other numbers formed higher voltage than that. The pole was designated as the potential maximum and was shown by a sign +. The English letters indicated lower voltage referred to a minimum shown by −. Each equipotential line was drawn every 0.05 and 0.2 mv at atrial activation and ventricular activation respectively.

The EPD during ventricular activation. The ECGs of the infants show a right axis deviation, abnormal degree of right ventricular preponderance, and changes in amplitude and direction of the T waves. Fig. 3 shows 6 limb-lead ECGs taken from a baby 2 days old. The rS wave in Lead I and aV_L suggests a typical infant pattern with the qR wave in Lead III and aV_R which means right axis deviation and right ventricular preponderance. This difference from the ECG in the normal adult caused a much different EPD in the newborn infant from that of the adult. The EPDs during ventricular activation in the baby whose limb leads are shown in Fig. 3 show the average pattern which could be seen in most of the infants (Fig. 4), although there were slight variations in the potential distributions among the infants.

The average patterns during ventricular activation were divided into five events phenomenally as follows.

1. In the early stage of ventricular activation, the maximum appeared on the sternum or slightly to the left of the sternum (Fig. 4A). The voltage gradient increased on the same site for a few seconds.

2. This early maximum shifted to the central precordium, while the minimum appeared on the right subclavicular wall (Fig. 4B) or on the left subclavicular wall in a few cases. Soon after that, the minimum shifted to the left subclavicular wall and the maximum shifted to the lower precordium increasing the voltage gradient (Fig. 4C). The minimum did not always appear on the left subclavicular wall, and appeared on the upper sternum in 2 infants. In this period, the maximum had the highest voltage on the anterior precordium.

3. The minimum on the left subclavicular wall increased its voltage gradient and spread widely over the left upper precordium, while the maximum was directed away to the right lower precordium, decreasing the gradient (Fig. 4D). The maximum had the pseudopod extension over the left lower precordium and the the right upper wall. In other infants, the pseudopod extension over the left lower precordium was more predominant than that of the right upper wall so the maximum occupied over the lower precordium including both the right and left lower wall. In several cases, the multimaxima that appeared on the anterior precordium, that is, one was on the right upper wall, another was on the left lower wall instead of the pseudopod extension.

4. After 25 to 35 msec. (Fig. 4E), the maximum continuously decreased its volt-

Figs. 4A through 4F. The electrocardiographic potential distributions in the baby whose ECG are shown in Fig. 3.

4 MSEC

Fig. 4B. For legend, see Fig. 4A.

8 MSEC

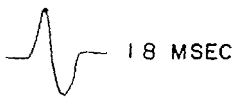


Fig. 4C. For legend, see Fig. 4A.

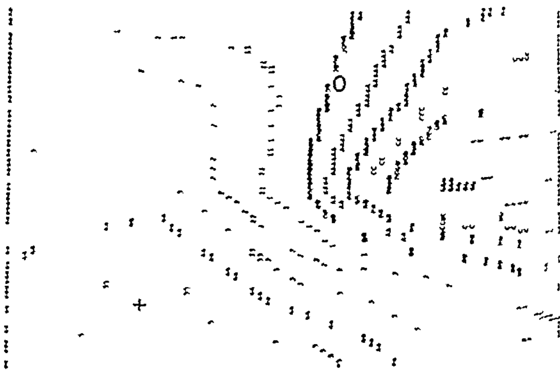


Fig. 4D. For legend, see Fig. 4A.

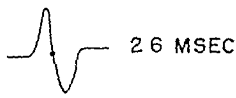


Fig 4E For legend, see Fig 4A.

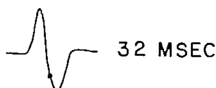
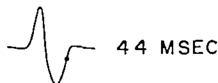




Fig 4F For legend, see Fig 4A.



age Shifting direction of the maximum was toward the right axilla from the right lower wall and then to the right upper precordium With this shift the minimum on the left wall moved to the central lower precordium with the same voltage or slightly higher than that of period 3. In 4 cases the maximum dropped to the lower precordium and did not clearly shift to the right axilla. In one of them the maximum shifted to the left lower precordium but it remained in the same site while the minimum ... and did not move to the left axilla ... more.

5 In the last stage of ventricular activation the maximum appeared on the upper precordium or the left upper wall and most of the precordium was occupied by the minimum ... the magnitude at the same ... (Fig 4F)

The variation with days The characteristic variations with days were also observed in subjects of more than one half of all the infants studied although there were differences between individuals to some extent. One series of 6 limb lead ECG with days are shown in Fig 5. The wave pattern of the aVR changed predominantly with marked ... of the T wave. Early stages of the QRS complex also showed slight changes although it was not marked. However the changes appeared in the FID shown in the following figures. Fig 6 shows the *variations with days* in the early stage of ventricular activation. The maximum occupying over the central to left precordium in the first day (Fig 6A) after birth was moved to the center or upper wall by the minimum which appeared first during the fifth (Fig 6A) to eighth day (Fig 6C) on the left precordium. The variations with days in the early stage of ventricular activation were characterized by the fact that the minimum inclined to appear with the passage of days over the left lower precordium to the left axilla. Generally it was rare for the minimum to appear over the left precordium in the earliest stage of ventricular activation during 1 to 2 days after birth while −0.1 to −0.4 mv minimum inclined to appear over the left lower wall after around 5 to 8 days. However the minimum over the left lower wall decreased its voltage with the progress of ventricular activation and disappeared when the different ... appeared over the right upper wall or the left upper wall in the period 1. Subsequently it was driven away completely by the maximum located over the upper precordium. This minimum corresponds to the Q wave appearing with days in the ECG from the left precordium measured by Walsh[7]. It also reflects the augmented r wave with days in Lead I.

The earliest minimum in period 1 appeared on the right subclavicular wall in most infants. In 4 infants however the minimum did not appear on the right subclavicular wall in the earlier days after birth but there were variations with days that the minimum appeared in the later part of the investigation.

At the period 2 when the minimum appeared over the upper anterior precordium including the left upper wall corresponding to the Q wave and the ascending leg of the R wave in Lead II, the maximum which appeared over the anterior precordium was inclined to shift to the left wall as the days passed. The shift of the maximum to the left wall was found in 3 FIDs shown with days in Fig 7 the sampling points of which were almost the same in the time reference ECG. In this period 2 the maximum appeared on the central precordium in 1 hour after birth (Fig 7A) shifted gradually to *the left precordium* with the passage of days (Figs *7B* and *7C*). The minimum appeared at last on the left axilla at 3 days (Fig 7C). However this minimum appeared again on the right lower precordium just after milliseconds. The change can be seen on the increased r wave with days in the aVL and the wave change of the aVR (Fig 5)

The FID during atrial activation The potential distributions in the stage of atrial activation were investigated from the onset of the P wave to onset of the Q wave. In earlier stages of the P wave in time reference ECG the minimum appeared at the right upper precordium and the rest of the precordium was occupied by the maximum (Fig *8A*). *With time*, the minimum spread over the central precordium from the right upper wall. The minimum with a voltage of about −0.1 mv had occupied the precordium from the

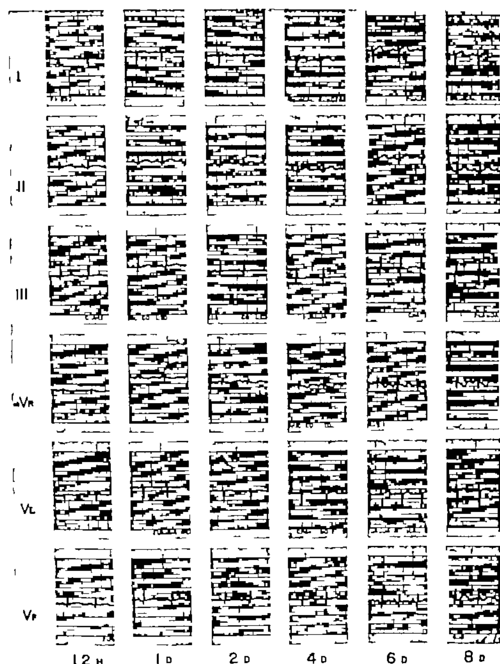


Fig. 5 Conventional limb-lead ECG at 12 hours, 1 day, 2 days, 4 days, 6 days, and 8 days after birth, from left to right.

end of the P wave to the onset of the Q wave in most infants (Fig. 8B)

Discussion

In the fetal period the peripheral vascular resistance in the systemic circulation greatly affects the right heart because of the large pulmonary resistance and the patent ductus arteriosus which remains open for a short time after birth. Therefore, it is said that the right ventricle is still preponderant after birth. This preponderance has been explained by the fact that the QRS complexes in the con-

Fig. 6A. Potential distributions at first day after birth of infant whose ECGs are shown in Fig. 4.

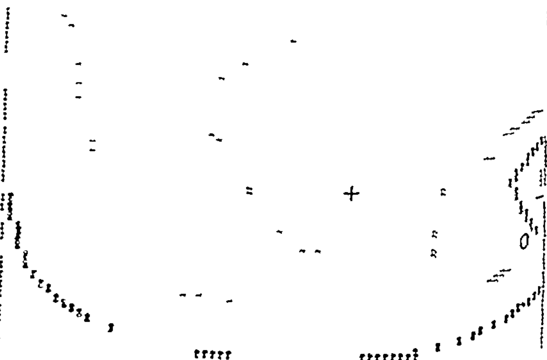


Fig. 6B. Potential distributions taken 3 days after birth in infant whose ECGs are shown in Fig. 3.

ventional ECG which were taken from the chest under influence of the right ventricle, have a relatively large magnitude. With progressive activation the maximum shifts from the lower precordium to the right (Figs. 4D and 4E) which indicates right ventricular preponderance clearly.

Immediately after birth the pulmonary venous return increases with the beginning of pulmonary respiration. The foramen ovale and ductus arteriosus then close both functionally and organically, although there is a left to right shunt of blood for a few days.[9, 11] Finally the left heart begins to work against the vascular resistance of the systemic circulation; therefore the load on the left heart is considered to increase with the passage of days, so that the left ventricle comes to preponderance. One tendency noted was that the maximum shifted to the left precordium in the earlier stages of ventricular activation (Figs. 7B and 7C) which seems to correspond to the increasing load on the left heart and the temporal left ventricular preponderance. Moreover the pseudopod extension of the maximum observed in period 3 when the maximum was located over right lower wall tended to spread over the left precordium with the passage of days. The fact might also show the increasing load to the left heart.

In adults the progress of activation in the heart moves toward the left and inferior area because of the thicker left ventricular wall and the distribution of Purkinje fibers, while in infants the maximum spread over the right precordium through the lower one and the minimum was located on the left wall. The direction of the progress was apparently toward right and inferior and then superior. This might also prove the right ventricular preponderance which means the right ventricular wall is anatomically thicker than the left one or at least equal. However, even in

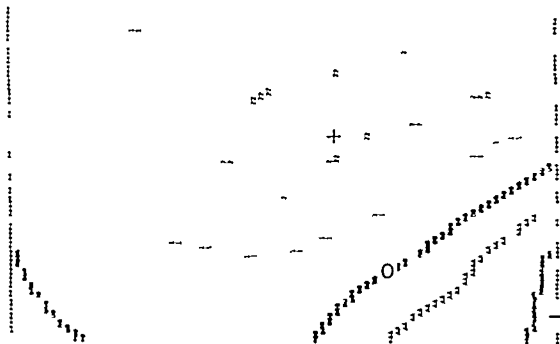


Fig. 4C. Potential distributions taken 5 days after birth in infant whose ECG are shown in Fig. 5.

Fig. 7A. Potential distributions at 12 msec. after the EP shown in Figs. 6A-6C at 12 hours after birth.



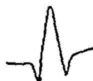


Fig. 7B. Potential distributions at 12 msec. after EP shown in Figs. 6A-6C taken the second day after birth.

the period when the right ventricle was preponderant (period 3) the pseudopod extension of the maximum which appeared over the right wall spreads over the left wall so that activation of the left ventricular wall appears to remain to some extent. Therefore, the infants potential distributions in this period were not always mirror images of those of the adults which may be regarded as complete left ventricular preponderance The ratio left right ventricle in adults was about 3 1 while it was fairly equal in infants. This anatomical "incomplete preponderance in infants compared with adults might cause the pseudopod extension spreading to both directions (the left lower wall and right upper one) at the same time.

In the last stage of activation the maximum appeared on the subclavicular precordium or the left upper wall (Fig 4F) The maximum in adults appeared again on the sternum where the earlier maximum appeared Then these maxima in the infant and adult might be caused by the same phenomena namely the last activation in the heart might occur at the cardiac base of the ventricle and ventricular septum.[11]

In atrial activation, the increase of venous return to the left atrium caused by pulmonary respiration should be considered Moreover there might be a great load on the right atrium induced by the open foramen ovale. Therefore the minimum appearing on the precordium in the period corresponding to the P R segment of the time reference ECG might show atrial hypertrophy or dilatation.

Summary

Electrocardiographic potential distributions were studied in newborn infants whose ECGs change rapidly with days corresponding to the hemodynamic vari-

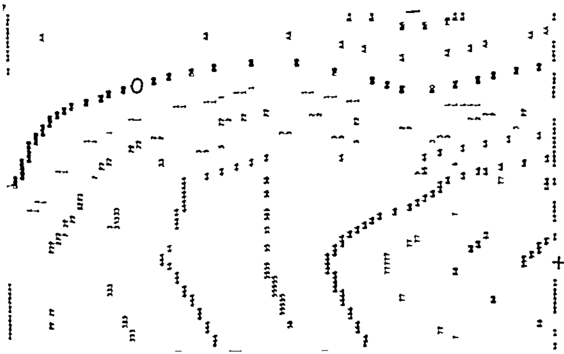




Fig 7C. Potential distribution at 12 msec. after EPD' shown in Figs 6A-6B taken the eighth day after birth.

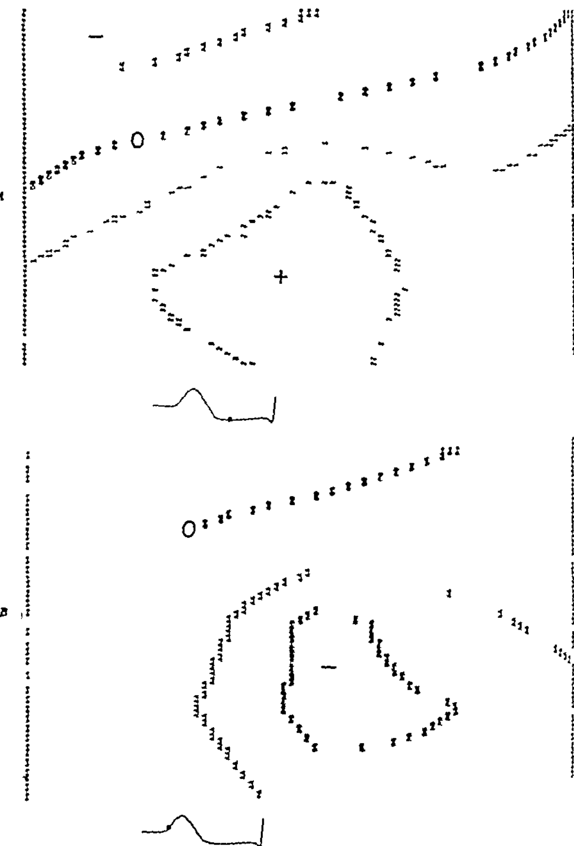


Fig. 3. The potential distributions during atrial activation.

ations and adaptations. Chest ECG s were taken from 25 explored points on the anterior precordium sampled every 2 msec. and quantitated by an average response computer A digital computer was also used to compute bilinear interpolating values between adjacent explored points and equipotential lines were printed on a line printer The investigating period was from 12 hours to 8 days after birth These potential distributions in infants were very different from those of adults and children, and showed clearly a pattern of right ventricular preponderance. This pattern could be seen during the investigating period but distributions which might show increasing load on the left ventricle and the left ventricular preponderance were observed in the latter days of investigation

We wish to thank Dr S. Goto and Dr M Shigematsu of the Hokumo Hospital, Sapporo, Japan, for the opportunity to perform this study and also M K. Takaya and Mr Y Mitamura of the Department of Medical Electronics for their help in recording the ECG and mapping the distributions.

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Intraventricular trifascicular blocks. The syndrome of right bundle branch block with intermittent left anterior and posterior hemiblock

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The four cases to be described below are the first reported in which conduction was impaired in the three main terminal fascicles (the right bundle branch and the two divisions of the left) of the intraventricular conduction system at the same time. These cases furnish evidence of the electrocardiographic patterns of block within the anterior and posterior divisions of the left bundle branch, which we have respectively termed left anterior (LAH) and left posterior hemiblock (LPH). At the same time these cases can also be considered as the prototype for a new, very peculiar, and as yet undescribed electrocardiographic syndrome.

Case report. Patient 1

This patient was a 58-year-old man [illegible] angina pectoris [illegible] subsequently developed heart failure and protracted Adams-Stokes seizures. During his admittance 20 electrocardiograms (ECG's) were recorded. He died a few days later, and an autopsy was obtained. For a better understanding [illegible] electrocardiographic evolution can be considered separated into four successive periods.

From June 3 to [illegible] 1959 (the first 25 days), [illegible] tracings were recorded, all of them displaying the pattern shown in Fig. 1, namely, right bundle branch block (RBBB) plus an anteroseptal myocardial infarction, and an ÂQRS at −75° [illegible] and the Q [illegible] in Lead I (QRS of the Q_1S_1 type) and the [illegible] S wave [illegible] the same lead.

From July 26 to Aug. 23, 1959, seven tracings were taken. The first three were like the one in Fig. 2, and the next four like the one in Fig. 3. Fig. 2 shows

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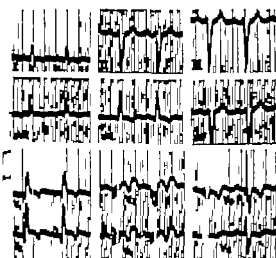


Fig 1 Patient 1 ECG of June 3 1950, showing RBBB with LAH and an anterior myocardial infarct. ÂQRS, −75° P-R interval, 0 16 sec. QRS interval, 0.12 to 0.13 sec.

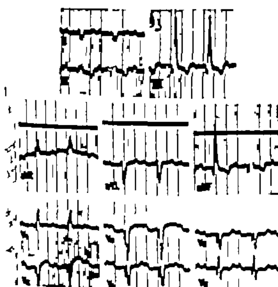


Fig 2. Patient 1 ECG of Aug 2 1950 showing RBBB with LPH, ÂQRS, +110° P R interval, 0.26 sec QRS interval, 0.12 to 0 13 sec.



Fig 3 Patient 1 ECG of Aug 7 1950, showing both types of beats in the same tracing, with changes in A-V conduction. In Leads I II and III the first two beats show RBBB with LPH the third P wave fails to be conducted and after the pause the fourth beat has shorter P-R interval and shows RBBB with LAH The fifth beat, with very long P-R interval shows again RBBB with LPH In aVF the first beat (after pause) shows RBBB with LAH the three which follow RBBB with LPH and longer P-R interval

again an RBBB pattern with an anterior myocardial infarction, but the ÂQRS is directed now at +110° Besides, the P R interval has lengthened to 0 23 to 0.26 sec in the three ECG of this subgroup. The QRS interval measures 0.12 to 0 13 sec., as before. The tracing can be considered an example of the infrequent cases of RBBB termed rare or uncommon type. The ECG in Fig 3 (representative of the last four of this group) exhibit both types of ventricular complexes in one single tracing concomitantly with changing A-V conduction (second degree A-V block). In Leads I II and III the first two beats have an ÂQRS at +110° the third P wave is nonconducted, and the fourth, after shorter P-R interval, yields a ventricular complex with an ÂQRS at −75° The next P-R interval is prolonged, and its ventricular response shows again an ÂQRS at +110° In aVF after pause (due to blocked P

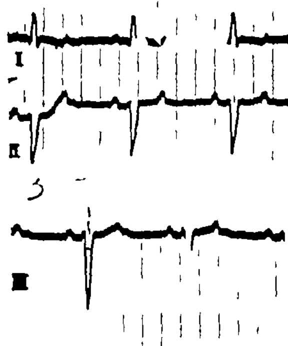


Fig 4 Patient 1 ECG of Sept 30 1950, showing RBBB with LAH and 2 1 AV block.

w / the first ventricular beat having AQRS at −75° and the next three with a longer P R interval, having AQRS at +110°

From Sept 7 to 30 1950 four ECG were recorded The ÂQRS pointed again at −75° and AV conduction was now permanently abnormal, changing from 1 1 and P R interval of 0 21 sec., to 2 1 and P R interval of 0 13 sec as illustrated in Fig 4

From Oct. 12 to Dec 13 1950 the last four tracings were recorded, all of them showing complete heart block, as illustrated in Fig 5 Since all the four cases reported in this paper exhibited essentially the same features, we prefer to discuss this case right now to facilitate the description of the other three.

Discussion Patient 1 The patient had first RBBB with an ÂQRS at −75° subsequently with RBBB always present the ÂQRS shifted to +110° concomitantly with the occurrence of important AV conduction disturbances. Both types of RBBB pattern could be observed many times in one single tracing Then after a period in which only the first type of QRS was again present, complete heart block developed The main problem is why or how could the patient have two different RBBB patterns sometimes with an ÂQRS at −75° some other times with an ÂQRS at +110° Since RBBB was present under both circumstances and at every moment behaved as being complete and irreversible it is plainly evident that during the generation of both types of QRS the sinoatrial impulse reached the ventricles through the left bundle branch only and that, on arriving first into the left ventricle two different conducting pathways were available. When the impulse followed one of them only left ventricular activation proceeded from below upward shifting the ÂQRS superiorly and to the left if the other was the one taken left ventricular activation proceeded from above downward turning the ÂQRS inferiorly and to the right. The important conclusion to be drawn is that, within the human left ventricle two independent conducting pathways do exist, and that these channels can either conduct or be blocked

Early in 1950 the authors believed that the two pathways could be one of them, the group of fibers described by Mahaim as connecting the upper part of the conducting system to the upper part of the ventricular septum[?] the other the left bundle branch itself However as soon as enough was learned about the distribution of the left bundle branch system in different animals and in man it became very clear to us that those two pathways could be nothing else but the two main divisions of the left bundle branch (Fig 6) This became even more obvious when block in those two divisions was produced experimentally in dogs[?] either single or combined with RBBB

Therefore the patient had permanent RBBB plus unstable or intermittent block in the two divisions of the left bundle branch In the first series of tracings (Fig 1) the posterior division conducted normally (on account of which the P R interval was normal) while the anterior division failed to conduct. Thus, the sinoatrial impulse reached the left ventricle through the posterior division only Ventricular activation thus began in the posterior wall of the left ventricle and progressed from that posterior inferior or diaphragmatic wall towards the anterolateral wall, shifting the ÂQRS superiorly and to the left When the second series of tracings (Fig 2) was recorded a conduction derangement had

supervened within the posterior division in a higher degree than the one previously present in the anterior division. Therefore the impulse arrived now into the left ventricle through the anterior division reaching first its anterior wall from where activation started advancing towards the posterior or inferior wall deviating the ÂQRS inferiorly and to the right. Since the anterior division was also involved it is understandable that such a change in the order of ventricular activation be accompanied by a delayed A V conduction time which changed from 0.16 sec. in the first group of ECG's to 0.23 to 0.26 sec. in the second

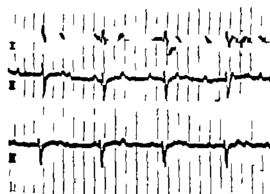


Fig 3 Patient 1 ECG of Dec. 13 1950, showing complete heart block.

We come now to the period in which both types of RBBB could be observed side by side in one single tracing always in correspondence with gross changes in A V conduction (Fig 3) What happens here puzzling as it may look is not so difficult to understand in its general essence. The impulse on arriving into the left ventricle reaches a crossroad from where two conducting pathways, though both altered can be utilized Small variations of the conductivity in each or in both will evolve different possibilities encompassing all possible combinations of either first, second, or third degree block in one fascicle, with either first, second or third degree block in the other fascicle The same problem has previously been considered in cases of bilateral bundle branch block.[7-11] In the latter case the problem concerned specifically the two main bundle branches, right and left. In the present case, the two pathways ready to share the distribution of the impulse are the anterior and the posterior divisions of the left bundle branch Thus, it is not so difficult to understand that a high score of combinations of different forms of intraventricular and atrioventricular conduction may originate [23]

In Fig 4 block became complete and permanent in the anterior division while conduction within the posterior division though very much impaired was still possi



Fig. 4 Left septal surface of a human heart, after removing the endocardium and dissecting the left bundle branch system. The main stem of the left bundle branch emerges in the subaortic region Its main divisions, anterior and posterior can be seen, heading for their respective papillary muscles.

ble. Finally conduction ceased completely in the posterior division too this la t event necessarily bringing in its wake a complete heart block (Fig 5) In fact this was to be expected considering that the main terminal fascicles of the intraventricular conduction system g ive all clear evidences of being seriously damaged However it should be observed that this he irt l lock is concerning its mechanism quite a new affair Neither the A V n ode and main l undle nor the two bundl l ranches (at least not the stem of the left l undle branch) participate in its produ tion This heart l lock is due to lesions in the right l undle branch on the one l and and t lesion in the two divisions of the left in th other It is neither mono- nor l ifascicular It is a trifascicular h art l lock.

According to this interpretation the ECG of Fig 1 is an example of the association of RBBB with LAH and that of Fig 2 the association of RBBB with LPH This conclusion is extremely important because (1) It makes manifest the existence of LAH and LPH in the human being (2) it serves to illustrate their electrocardiographic patterns when combined with RBBB (3) it shows both hemil locks in the same patient and sometimes even in one single tracing i e under equal cardiac and extracardiac conditions.

Case report Patient 2

Thi patien w oung man w th f th developed picture of hronic Chagasic m ocarditis. No other information w lable

From J uary 1944 t November 1947 ECG were recorded The one in Fig 7 dated Sept. 28 1946 show essentially RBBB pattern ith an ÂQRS t −60° namely from what w le rned in the case of P tient 1 RBBB with LAH The QRS interval measures 0 16 sec and there is trial fibrillation. A ery mall Q e is present i Lead I nd in the chest leads, Q wave l V smaller in V nd lmost vanishing V suggests a teroapical necrosis. Two previou ECG (not show) were similar but with some interesting differences. One from Jan. 21 1944 the first t be recorded on the patient, showed a sinoatrial rhythm with P R interval of 0.16 sec. RBBB with LAH were already present, but the S waves were much less deep in Leads II and III and much more conspicuous in Lead I (the ÂQRS wa directed t −90° instead of −60°). Another one from March 20 1946 was inter

*The ECG' of this patient are published in 1949, in paper by Ramos and associates[30] In 1945 as one of us was lab- ing Sao Paulo, Dr. Jairo Ramos was kind enough to let us have the original tracings.

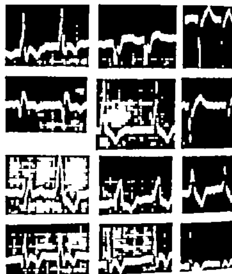


Fig 7 P tient 2 ECG of Sept. 28 1946 sh w RBBB w th LAH ÂQRS bout −60° QRS l 0 16 sec. Atrial fibrillation

mediat the S w became deeper in Leads II and III nd less noticeable in Lead I According to our poi t of view the patient had RBBB ith LAH hose degree wa incre ing (that of the LAH) i.e. LAH as incomplet in the first tw tracings.

The ECG of Fig 8 as recorded on Apr 21 1947 seven month fter that of Fig 7 There a ... change in the ÂQRS direction, hich shifted from −60° to +120 — t rn of 180° downward and to the right. The QRS complex changed from a Q S to S Q type 1 spite of ll this the chest leads ... show the presence of an RBBB pattern ... large oltage of the R w ... Leads II and III ... nd 3.8 m respectively), and that the Q wave ... ha been obliterated from V t V The QRS width is till 0 16 sec. I hort with RBBB al...present, the initial p ttern f LAH ha vanished, and ... tern of LPH ha taken its place meaning that ... impairment of conduction ithin the posterior division of the left bundle branch has evolved ... tively greater degree tha the one previously ... within the terior division. The presence of atrial fibrillation precludes the observation of the changes in A V conduction hich ere t be expected ... Patient 1 Some of the QRS changes in the chest leads are ttributable to the substitution of LPH for LAH the most importa t being the disappearance of the Q es from V t V

Case report Patient 3

This as a 60-year-old oman ith Adams-Stokes seizures tarting for months prior to her admission nd no other symptoms or signs. Her blood pressure was normal and on -ray examination her heart looked normal or only slightly enlarged. After a few month w lost sight of her and no definite diagnosis was accomplished. Though one cannot rule out either coronary heart disease or some sort of ...

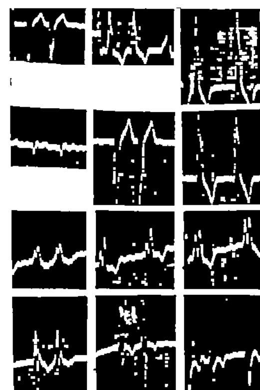


Fig. 8 Patient 2, ECG of Apr 23 1947 showing RBBB ith LPH ÂQRS, +120° QRS interval, 0 16 sec. Very tall R wa ves in Leads II and III Disappearance of the Q wa ves from V t V as compared to Fig 7



Fig 9 Patient 3, ECG of Sept. 14 1959 showing RBBB with LAH and 2 1 A-V block ÂQRS, −45° QRS interval, 0 15 sec. P R interval, 0 32 sec.



Fig 10 Patient 3 ECG of Oct. 24 1959 showing RBBB with LPH and 1 1 A V conduction ÂQRS +110° QRS interval, 0 17 to 0 18 sec P-R interval, 0 20 sec. Very tall R waves in Leads II and III As compared to Fig 9 the Q wav has vanished from V to V.

cardial disease most probably she had primitive degenerative process of the intraventricular conduction system, of the type described by Lenegre[14] (see later).

From Aug 6 t Nov 25 1959 35 ECG were recorded These showed permanent RBBB and conduction disturbance in the tw divisions of the left bundle branch, varying within each of them between first and second degree block ith different grades of synchrony or asynchrony in such manner that, hole score of different QRS patterns and sequences of them occurred, some of these patterns looking like fusion beats of the LAH and LPH contours.

Fig. 9 show tracing recorded on Sept. 14, 1959 in hich, like in the first six ECG taken from Aug 6 t Sept. 22, 1959 the entricular comple as of the RBBB ith LAH type. The ÂQRS points at −45° and the QRS interval measures 0.15 sec There is 2 1 A V block and the conducted beats are preceded by P-R interval of 0 32 sec Note the small Q ves from V t V The P-P intervals ranged between 0 80 and 0.95 sec. along the whole tracing Fig. 10 show tracing taken on Oct 24 1959 That day the sinoatrial rate as lower (P P intervals bet een 1.06 and 1 16 sec), because of hich V-V conduction was 1 1 ith P R in-

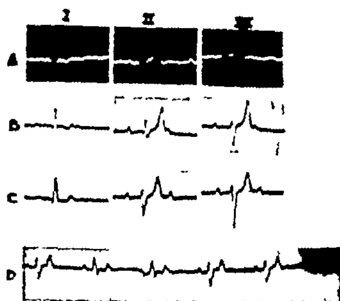


Fig *11* [illegible] ECG of Aug. 6 1959 *B* ECG of Sept 10 1959 *C* ECG of Sept. 19 1959 *D* ECG of Sept. [illegible] 1959 The [illegible] three strips show progressively increasing degrees of LAH (also [illegible] RBBB. The ÂQRS [illegible] from [illegible] in [illegible] to −20° in *B* and to −60° in C. As the degree of LAH increases, S_1 and [illegible] grow larger and [illegible] R in Lead III tend to disappear. In strip C RBBB masquerades as LBBB. In *D* the degree of LAH [illegible] changing in the same strip (Lead II) in the presence of 2 1 A-V block.



Fig *12* Patient 3 [illegible] 1 A-V block sets in increasing the R-R intervals, there is a reduction of the QRS voltage, indicating change in the degree of the LPH

terval of 0.20. In contrast to Fig 9 the ventricular complex is now of the RBBB with LPH type with the ÂQRS pointing at +110° and the QRS having changed from a Q S_1 to [illegible] S_1 Q type. The QRS interval has widened to 0.17 to 0.18 sec Note the very tall R waves in Lead II and III (2.4 and 2.9 mv., respectively), and also the obliteration of the Q waves from V_1 to V_4.

Fig 11 (four selected strips of as many ECG taken in different days) illustrates the occurrence of different degrees of LAH. The upper strip (*A*) is from a tracing of July 6 1959 a day in which the sino-atrial rate was very low (P-P intervals of 1.30 sec.) The P R interval measures 0.23 sec. and the QRS 0.15 to 0.16 sec. A-V conduction is 1:1. *The ÂQRS is at 0°* The next strip (*B*) is from [illegible] tracing of Sept. 10, 1959 a month later and the second ECG taken on the patient. That day the sinoatrial rate was higher (P-P intervals between 0.80 and 1.00 sec.) and A-V conduction was 2 1 with a P-R interval of 0.34 sec. *The ÂQRS is at −20°* Four days later (Fig 9), the *ÂQRS is at −45°* and after another few days, on Sept. 19 1959 (*C* of Fig 11), with a P-R interval of 0.30 sec. and 2:1 A-V conduction

the ÂQRS is at −60° The greatest degree of LAH as compared to all the previous tracings, has been reached. The fourth strip (*D*) is Lead II from trac ing on Sept. 22, 1959 three day after the previous one, and constitutes direct proof of the ÂQRS shifts being really due t conduction changes within the anterior division of the left bundle branch and not to positional variation of the heart. I the same lead, the ÂQRS ranges from −20° to −60° the degree of LAH increasing after shorter cycles and decreasing after longer ones. The degree of LAH is changing against a constant background of RBBB

Varying degrees of LPH are show in Fig 12 at moment hen A-V conduction was changing from 1 1 to 2 1 As can be appreciated, the degree of LPH decreases (there is a general decline in the QRS voltage, mainly affecting the R aves in Leads II and III but also the S wave in Lead I) as the R-R intervals grow larger

Variations in the degree both of LAH and LPH were shown in Figs. 11 and 12, but strictly speaking, there are two manners in which those changes can be accounted for: one, as stated, by true changes in the degree of either one or the other hemiblock the other through changes in the degree of synchrony with hich conduction is taking place in both divisions of the left bundle branch at the same time It seems very likely that such combinations occur hen the conduction delay in both the anterior and posterior divisions of the left bundle branch are of similar magnitude, and chronologically overlapping each other I the case in which the two conduction times are equally prolonged, the corresponding QRS complex will show neither LAH nor LPH for left ventricular activation will keep its normal sequence and synchrony

Case report Patient 4

This patient was an 80-year-old man with angina pectoris, arterial hypertension, congestive heart failure, and grossly enlarged heart. A few Adams-Stokes seizures had occurred in the last time. From Dec. 16, 1959 to June 29 1963 four ECG had been recorded.

Fig 13 corresponds to the first tracing, of Dec. 16, 1959 (the second one, on Sept. 30, 1961 was identical). It can be considered as an example of RBBB ith LAH with an ÂQRS at −70° An associated inferior all infarction cannot be definitely excluded The P-R interval measures 0.20 sec. and the QRS interval 0.13 sec. in the standard and 0.16 sec. in the chest leads.

Fig 14 corresponds t the fourth tracing of June 29 1963 (the third, on May 10, 1963 was ery similar). It is typical example of RBBB with LPH The ÂQRS has shifted from −70° to +110° Accompanying this change, the P-R interval has lengthened from 0.20 to 0.28 sec. There is Q in V and V and none in the left precordial leads. As in Patients 1 to 3, we hav here again change from LAH to LPH against constant background of RBBB, concomitantly with disturbances in A-V conduction

When the fourth ECG was taken, ery long tracing as obtained until series of changes in conduction could be detected. For instance, the top strip in Fig 15 illustrates phenomenon already

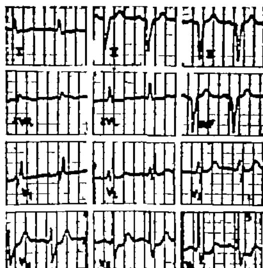


Fig 13 Patient 4 ECG of Dec. 16, 1959 showing RBBB with LAH ÂQRS, around −70° P-R interval, 0 20 sec QRS interval, 0 13 sec.

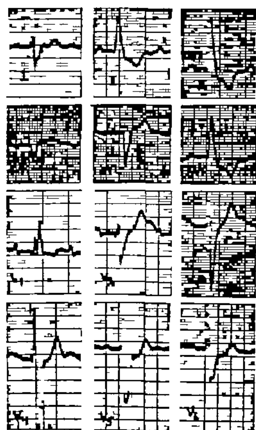


Fig 14 Patient 4 ECG of June 29 1963 showing RBBB with LPH. ÂQRS, around +110° P-R interval, 0 28 sec. QRS, 0 13 sec As compared to Fig 13 the Q was disappears from V and V₄.

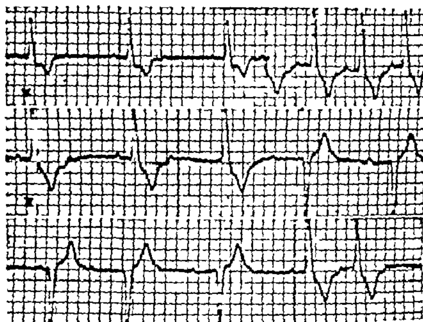


Fig. 15 ... When A-V conduction changes from ... with great shortening of the R-R intervals, the degree of LPH augmentation is expressed by a marked increase in the voltage of R. *Middle and bottom,* continuous strip of lead III. Both types of QRS (RBBB with LAH and RBBB with LPH) in the same tracing. The ... three beats and the last two show RBBB with LAH; all the others RBBB with LPH. None of the beats ... ventricular escapes. ... A-V conduction changes.

shows ... the previous ... When A-V conduction changes from 2:1 to 1:1 and the R-R interval shortens accordingly, the R wave becomes considerably taller in Lead III, indicating an increase in the degree of the LPH. Finally, the two lower strips in Fig. 15 show beats with LAH or LPH in the same tracing. It can be assumed these beats are not escapes since their morphology is similar to the one recorded during LAH (Fig. 13) and LPH (Fig. 14). In addition, there is second degree A-V block within both divisions. Both types of QRS do appear together with very typical changes in A-V conduction, including P-R intervals up to almost 1.00 sec.

Discussion

The four cases above described all have in common the presence of permanent RBBB, intermittent LAH and LPH, and as a consequence of these important A-V conduction disturbances. Though what undoubtedly gives the peculiar touch to this syndrome is the intermittent LAH and LPH, a complete account of all its features is in order. This in turn shall serve as ground for discussing in the second part of this paper[33] the whole group of syndromes that we have named "intraventricular trifascicular blocks,"[11] of which the one we are now considering is but a variety.

The syndrome of right bundle branch block with intermittent left anterior and posterior hemiblock

THE RIGHT BUNDLE BRANCH BLOCK. In the four cases, RBBB seemed to be complete, permanent, and irreversible. An obvious question is thus whether or not such completeness—or the mere presence of RBBB—is an indispensable requirement for the syndrome to occur or to be acknowledged; in other words, whether it is possible or not for a case of intermittent LAH and LPH to exist with RBBB ... with no ... RBBB ... the literature[11,12] but we could find none in which RBBB was completely absent. This observation was at first baffling, but at a later time the reasons for it became apparent. These will be considered briefly here. The posterior division of the left bundle branch is the least vulnerable or most unyielding segment of the whole intraventricular conduction system,[7] so that whenever LPH occurs, be it permanently or intermittently, it is very unlikely for the other segments to have remained undamaged. In fact, *LPH is usually preceded either by RBBB, LAH, or both.* Thus, it is not

mere chance that in the four presented cases RBBB and LAH were always present from the start—at least from the very first tracing taken on each patient—whereas, LPH was regularly the last conduction disorder to become apparent.

THE INTERMITTENT LEFT ANTERIOR AND POSTERIOR HEMIBLOCK. The most consequential as well as peculiar electrocardiographic feature of the syndrome is the occurrence in the same patient, of two completely opposite directions of the ÂQRS always around an axis parallel to Lead III in such a way that when the electrical forces point superiorly the ÂQRS is at about −60° and when inferiorly at about +120° This feature is the key to the syndrome the key which permits, and demands to introduce the concept of the hemiblocks of the left bundle branch as an important event within the field of intraventricular conduction disturbances. In fact we have already seen that LAH is the one which deviates the ÂQRS to −60° and LPH to +120° These two opposite ÂQRS directions are hemiblock-dependent and unrelated to the RBBB which intervenes only as a configurational background

A strict requisite for the syndrome to take place is that both LAH and LPH be unstable or intermittent If conduction were completely interrupted in both divisions of the left bundle branch a LBBB would result. If conduction were intermittent in one division only and normal in the other the corresponding hemiblock would only appear intermittently And if conduction were intermittent in one division and totally interrupted in the other the ECG would basically show a hemiblock of the interrupted division and in addition LBBB beats (or nonconducted P waves, if the right bundle branch is also interrupted) However if as required by the syndrome conduction in both divisions is only partially impaired and there are changes in their comparative degree of block the electrocardiographic patterns due to block of each of the two divisions will be able to appear intermittently in the same patient such as actually happened in our four cases.

Conduction being unstable in both divisions of the left bundle branch the degree of block may change either in one division while being held constant in the other or in both at the same time. In either case the differences in the conduction times of both divisions will be able to vary from very slight (or none) to more or less considerable and to the same extent will vary the degree of asynchronism in the activation of the anterior and posterior walls of the left ventricle. Both mechanisms can thus give place to variations in the electrocardiographic degree of either LAH or LPH including QRS contours of what we may confidently call "incomplete" hemiblocks. In fact, all this seems to have occurred in the above reported cases.

THE ATRIOVENTRICULAR CONDUCTION DISTURBANCES Inasmuch as the syndrome comprises block permanent in one fascicle and intermittent in two others, its natural evolution towards advanced or complete heart block cannot come as a surprise Out of the four presented cases, Patient 1 developed complete heart block, and Patients 3 and 4 a high degree A V block. Only Patient 2 failed to show A V block probably because of the presence of atrial fibrillation. The type of heart block presented in this communication is really *trifascicular* It is due to lesions of the three main terminal fascicles of the intraventricular conduction system namely the right bundle branch and the anterior and posterior divisions of the left branch

During the stage when A V conduction is not yet completely interrupted very interesting relationships arise between the A V conduction abnormalities and conduction within both divisions of the left bundle branch. Since block is permanent in the right bundle branch and only intermittent in the two divisions of the left, it must be clear that many of the A V conduction disturbances may be the exteriorization of the impaired conduction within those two divisions. Thus, in every case (but Patient 2 because of the presence of atrial fibrillation) the change from LAH to LPH or vice versa was unfailingly accompanied by a substantial variation in A V conduction and this was particularly noticeable when the changes occurred in the same tracing Now if one hemiblock pattern yields to the other it is because conduction varies within one division of the left bundle branch as compared to the other Therefore it may be inferred that those A V conduction vari

ations express the conduction changes in one division with respect to the other. For instance, if there is LAH with a normal P-R interval, it is clear that the P-R lengthening is measuring the impaired conduction within the anterior division. Accordingly, in every case but the second one first, second, or third degree block could be shown to occur in either one of the two divisions of the left bundle branch. Therefore, from the electrophysiological standpoint, the two divisions may behave like any other fascicular segment of the conduction system.

Inasmuch as the two divisions of the left bundle branch can sustain a first, second, or third degree block, which in addition may change under different circumstances, the most intricate and bizarre combinations of atrioventricular and intraventricular conduction disturbances can occur.

CLINICAL SIGNIFICANCE. Since the syndrome of RBBB with intermittent LAH and LPH presupposes the existence of abnormalities in three different parts of the intraventricular conduction system, it is expected to be related to significant disease of the interventricular septum. In our four cases the clinical diagnosis was coronary heart disease in two, chronic Chagasic myocarditis in one, and undetermined in the remainder. The small number of cases and the lack of autopsy data preclude more specific considerations. Nevertheless, the following points are worth taking into account. (1) If coronary arteriolosclerosis were really more common than up to now admitted,[11-4] it could be a good candidate to elicit the syndrome. (2) To provoke the syndrome, a myocardiopathy has to be a "panmyocardiopathy." In that sense, chronic Chagas myocarditis because of being the most typical of all panmyocarditis[28] offers the best possibilities. (3) To the present time, the existence of disease affecting exclusively or prevalently the specific tissue of the conduction system has not been proven. However, Lenegre has recently contributed very convincing evidence for a degenerative process of unknown origin solely striking the intraventricular conduction system.[14] Such a process, which we have termed "Lenegre's disease,"[1] must certainly be a good contestant in the list of diseases producing the syndrome of RBBB with intermittent LAH and LPH. In fact, in our Patient 3 that possibility was very likely.

From a clinical point of view and disregarding the causal disease, the only genuine characteristic of the syndrome is, as already commented upon, tendency to evolve a high degree or complete heart block with its known complications. If we were able to follow more cases of complete heart block from their initial stages, more cases of the syndrome of RBBB with intermittent LAH and LPH could probably be detected.

Summary

When conduction is interrupted in the right bundle branch and only intermittently in the two divisions, anterior and posterior, of the left, a very peculiar and as yet undescribed electrocardiographic syndrome occurs. Its main feature is the presence of two different right bundle branch block patterns with completely opposite directions of the ÂQRS (superiorly and to the left in one, inferiorly and to the right in the other), together with severe A-V conduction disturbances. Four cases of this singular syndrome are here described and analyzed. Such cases can be considered exceptional experiments of nature providing most invaluable evidence for the existence of block within the anterior and posterior divisions of the left bundle branch. However, the syndrome of right bundle branch block with intermittent left anterior and posterior hemiblock is only one of the several possibilities of what we have named "intraventricular trifascicular blocks," which will be considered in the second part of this paper.

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Cardiac and peripheral vascular effects of digitalis in clinical cardiogenic shock*

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Digitalis is often administered to patients with cardiogenic shock on the assumption that the drug will improve myocardial contractility and thereby increase peripheral blood flow. Although digitalis exerts an inotropic effect on the human heart and increases cardiac output in congestive heart failure[2] and experimental cardiogenic shock, its efficacy in clinical cardiogenic shock has not been clearly established.

In evaluating the circulatory responses to digitalis preparations, their direct arteriolar and venoconstrictor properties also must be considered.[1] Little clinical significance has generally been attributed to the peripheral vascular action of digitalis, but in the treatment of cardiogenic shock these vascular effects could be of particular importance. The pressor effect of arteriolar constriction might be beneficial in a hypotensive patient, but at the same time increases in left ventricular pressure work in the presence of profound impairment of cardiac function could aggravate heart failure.

In the present study the hemodynamic effects of intravenously administered cardiac glycosides were studied in patients with shock accompanied by evidence of heart failure (cardiogenic shock).[1] Catheterization of the left ventricle in some of the patients made it possible to directly assess changes in left ventricular performance. The vasoconstrictor property of the drugs was evaluated by analysis of the time course of changes in arterial pressure, myocardial function, and peripheral vascular resistance.

Methods

Studies were performed in 13 patients who fulfilled the diagnostic criteria for cardiogenic shock. These included the demonstration of inadequate peripheral blood flow and organ perfusion associated with a significantly elevated central venous pressure and/or left ventricular end-diastolic pressure. Evidence of inadequate blood flow included cold, clammy skin, oliguria, disturbances in mentation, or lactic acidosis. Auscultatory blood pressure

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Table I Clinical data in patients with cardiogenic shock

Patient	Age Sex	BSA	Diagnosis	BP†	L/P‡	Result
J P	56, M	1 45	Myocardial infarction	86/60	22 8/3 4	Died 10 days later
L W	72, M	1 83	Myocardial infarction	90/45	58 3/7 2	Died next day
L. B	54, M	2 10	Hepatic failure	75/50	—	Died 3 days later
F R	58, M	1 70	Pancreatitis	68/52	—	Died next day
F W	75 M	1 80	Pulmonary embolism	80/60	—	Survived
W B.	61 M	—	Myocardial infarction	0	27 0/2 4	Died same day
W H.	39 M	1 67	Septicemia	0	—	Died same day
L. E.	53 M	1 94	Septicemia	0	13 4/1 8	Survived
A. P	45 M	1 59	Cirrhosis, carcinoma	70/48	—	Died next day
G R	72, M	1 45	Myocardial infarction	90 (palp)	6 3/1 3	Died 25 days later
R. B.	48, M	2 48	Pneumonia	100/78	—	Survived
H. O	70 M	2 14	Cerebral thrombosis	0	32 7/1 7	Died same day
R H	79 M	1 82	Myocardial infarction	0	39 8 3 8	Died next da

*BSA, Body surface area in square meters.
†BP Auscultatory blood pressure (mm. Hg) at time of study
‡L/P Arterial lactate/pyruvate (mg. per cent).

was reduced or absent in all the patients although intra-arterial pressure was within the normal range in a few Arterial lactate levels[10] measured in seven patients averaged 28.6 mg per cent (normal 3 to 9 mg per cent) and lactate pyruvate ratios averaged 9 7 1 (normal 5 1) [11] Clinical data on these patients are shown in Table I Four of the patients had been on treatment with digitalis prior to the onset of shock

Hemodynamic studies were performed at bedside as soon as possible after the diagnosis of shock was established The femoral artery and vein were cannulated percutaneously by the Seldinger technique and polyethylene catheters were advanced into the right atrium and aorta. In 6 patients the left ventricle was entered by retrograde catheterization using a Siemens portable image intensifier fluoroscopy unit. Left ventricular aortic, and right atrial pressures were recorded using Statham P23Db strain gauge transducers positioned with zero level at the midchest and a multichannel Sanborn direct writing recorder The first derivative of the left ventricular pressure (LV dp/dt) was recorded using an RC differentiating circuit. The maximum pre-ejection dp/dt also was calculated from left ventricular pressure contours recorded at 100 mm. per second

Cardiac output (CO) was determined by the indicator dilution technique with injection of 5 mg of indocyanine green dye into the right atrium while aortic blood was withdrawn through a Gilford cuvette densitometer Total systemic vascular resistance (SVR) left ventricular stroke work (LVSW) and central blood volume (CBV) were calculated as previously described.[12] Left ventricular ejection time (LVET) was measured from the aortic pressure tracing and mean systolic pressure was obtained by planimetry The mean systolic ejection rate (MSER) was calculated by dividing the stroke volume by the LVET Tension time index was determined by multiplying the mean systolic aortic pressure by the LVET and the heart rate.[13] Statistical analysis was carried out using the t test.[14]

Results

Control hemodynamics (*Table II*) Systolic aortic pressure in the 13 subjects ranged from 60 to 136 mm. Hg and averaged 93 mm. Hg In those patients with systolic pressures over 100 mm. Hg the blood pressure measured by cuff always was considerably lower (Table I) Right atrial pressure (RAP) averaged 8.8 mm Hg and left ventricular end-diastolic pressure (LVEDP) measured in 6 patients, averaged 17 mm. Hg

Control CO ranged from 0 87 to 7 65 L. per minute and averaged 3 95 L. per

Table II Hemodynamic effects of digitalis in 13 patients with cardiogenic shock

Patient	Drug (dose)	Time (min)	Aortic pressure (mm Hg)	Left vent pressure (mm Hg)	Right atrial pressure (mm Hg)	Cardiac output (L/min)	Systemic vascular resistance (dyn sec cm)	Heart rate (beats/min)	Stroke work (gm M)
J P	Ouabain (0.5 mg)	0	92/61(70)		9 5	2 11	106	114	16
		60	100/64(72)		8	48	2060	117	19
L W	Ouabain (0 25 mg)	0	6/44(56)	6 17	8 5	3 02	1260	114	16
		5	94/58(70)	96/28	12	3 06	1316	114	21
L. B.	Deslanoside (0.6 mg.)	0	86/42(55)		8	4 72	796	48	63
		43	80/40(56)		6	5 90	678	48	83
F R	Deslanoside (1 0 mg.)	0	96/52(67)		7	5 32	902	114	38
		20	110/56(76)		3	5 65	1061	110	52
F W	Ouabain (0.5 mg.)	0	96/32(64)	96/3	10	5 87	737	55	49
		15	100 60(66)	112/0	8	5 45	852	83	52
W B	Ouabain (0.25 mg)	0	140/90(98)	136/14	3 5	1 9	42.6	126	18
		50	170/96(110)	160/16	7	—	—	114	—
	Ouabain (0.25 mg.)	56	176/92(114)	170/20	6	2 19	3910	114	28
W H.	Deslanoside (0.8 mg)	0	60/32(48)		10	3 30	870	114	13
		35	72/40(56)		8	4 29	897	135	70
L. E.	Ouabain (0.75 mg)	0	112/66(80)	122/14	7 5	4 79	1237	138	42
		20	130/72(90)	148/14	9	3 57	1680	114	33
A. P	Deslanoside (1 0 mg)	0	82/54(64)		11	7 65	551	120	54
		35	92 56(66)		10 5	8 01	558	102	60
G. R	Ouabain (0.125 mg)	0	118/76/(92)	121/30	11 5	8	7569	102	13
		20	126/80(98)	130/28	9	1 26	5570	74	21
R B.	Deslanoside (1.0 mg)	0	86/56(64)		12	5 31	752	72	37
		23	102/62(73)		11	6 54	758	103	57
H O	Digoxin (1 0 mg)	0	100/60(74)		11	4 00	1260	96	33
		4	128/72(90)		11	4 45	1405	102	47
		31	110/62(78)		8	4 63	1210	101	46
R. H.	Ouabain (0.25 mg)	0	82/52(56)	60/22	4 5	2 24	1810	96	11
		37	90/56(60)	74/20	2 5	2 31	1831	144	1

minute. The cardiac index was less than 2.5 L. per minute in all but 3 patients (F R. F W., and A. P) 2 of whom had chronic alcoholism and cirrhosis. The heart rate averaged 106 beats per minute. SVR averaged 1,850 dynes-sec.-cm $^{-4}$

The 5 patients with shock following acute myocardial infarction exhibited the most severe degree of myocardial impairment. CO averaged 2 05 L. per minute in this group and stroke volume only 17 ml. The LVEDP measured in 4 of these patients averaged 21 mm Hg but the RAP averaged only 7.5 mm Hg and was within the normal range in two of the five subjects. Despite the markedly reduced CO in this group arterial pressure was supported at nearly normal levels by an increase in SVR to an average of 3 400 dynes-sec.-cm.$^{-4}$ Systolic aortic pressure averaged 99 mm. Hg and mean arterial pressure 74 mm. Hg

Response to digitalis Following control observations cardiac glycosides were administered intravenously over a period of one half to one minute. Eleven injections were given to the 9 patients who had not been on maintenance digitalis therapy Five received deslanoside 0 6 to 1 0 mg 3 received four doses of ouabain, 0 25 to 0.75 mg and one was given 1 0 and 0.5 mg doses of digoxin The 4 patients who had been receiving oral digitalis prior to the onset of shock were given five doses of ouabain 0.125 to 0.25 mg

ARTERIAL PRESSURE. Aortic or left ventricular systolic pressure usually rose within one minute after infusion of digitalis and was increased above control levels in all 13 patients within the first 5 minutes (Fig 1) The early rise in pressure was similar regardless of the digitalis preparation given Systolic pressure rose by an average of 13 4 mm Hg and mean aortic pressure monitored during the first 5 minutes in 12 patients increased by an average of 9 mm Hg

The blood pressure response following this initial pressor effect was variable. Arterial pressure rose further during the period of observation in some subjects but plateaued or fell slightly in others (Fig 1) Neither the initial nor later pressor effect appeared to be related to the level of the control arterial pressure

Three patients received another injection of digitalis one hour after the initial treatment. In 2 a small early pressor effect was

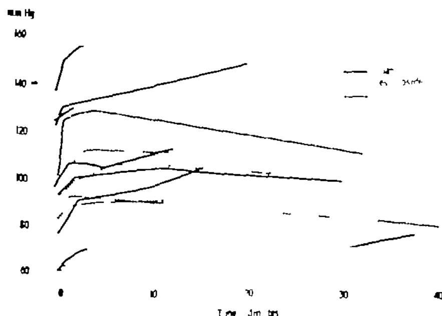


Fig. 1 Time course of changes in systolic pressure after intravenous administration of digitalis preparations to 13 patients with cardiogenic shock

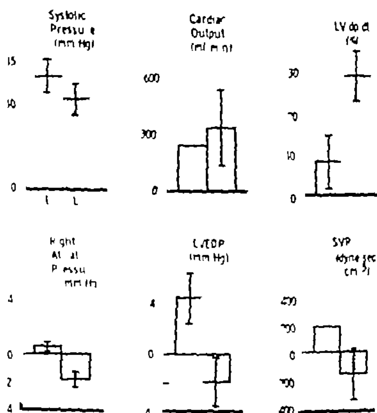


Fig 2 Average change from control during the early phase (*E*) (first five minutes) and late phase (*L*) (15 to 60 minutes) after intravenous administration of cardiac glycosides. Vertical lines indicate standard error

again noted but in the other patient a second injection of ouabain 0 25 mg did not alter arterial pressure

CARDIAC FILLING PRESSURE. RAP was not significantly altered during the first 5 minutes after digitalis. It rose sharply in one patient but remained essentially unchanged after the other 15 infusions (Fig 2) LVEDP monitored after administration of ouabain on seven occasions in 6 patients, increased during the early pressor phase from an average of 16 6 to 21.3 mm Hg ($p < 0.05$) This increase was due entirely to 3 subjects whose LVEDP rose precipitously following four infusions of ouabain from an average of 19.3 to 27.5 mm Hg

During the later phase from 15 to 60 minutes after injection of digitalis RAP fell in all but 2 subjects. RAP was reduced from an average of 8 8 to 7.2 mm Hg ($p < 0.05$) LVEDP was reduced in 3 of 5 patients studied during this phase (Fig 2) Later effects could not be evaluated on two occasions. In Patient L. W pulmonary edema developed as LVEDP rose to mm Hg during the early pressor phase and an infusion of isoproterenol was begun. In Patient W B the first injection of 0.25 mg ouabain produced an early rise in LVEDP from 14 to 20 mm Hg without apparent subsequent improvement. One hour later he was slightly improved but still in shock. Since he showed no signs of digitalis intoxication he was given another injection of ouabain 0.25 mg Within minutes there was a rise in LVEDP from 16 to 25 mm Hg followed by ventricular fibrillation and circulatory arrest.

CARDIAC OUTPUT AND SYSTEMIC VASCULAR RESISTANCE. CO was measured during the early pressor phase in only 2 patients. In Patient L. W CO and heart rate were unchanged after ouabain although mean aortic pressure was increased by 14 mm Hg The SVR therefore was increased from 1,260 to 1,520 dynes-sec.-cm. In Patient H O the CO four minutes after administration of digoxin had increased slightly from 4 00 to 4 45 L. per minute

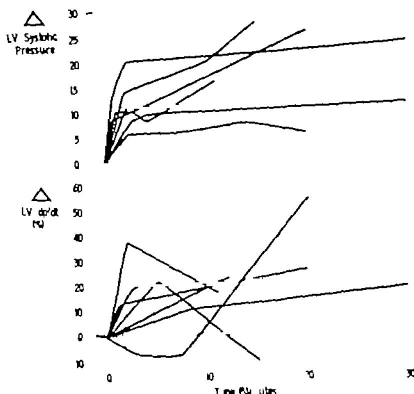


Fig. 3. Simultaneous changes in left ventricular systolic pressure and maximum pre-ejection dp/dt after seven injections of ouabain in 6 patients. The rises in pressure are not necessarily in phase with changes in dp/dt.

and the SVR rose from 1 260 to 1 410 dynes-sec.-cm $^{-5}$

In the later phase after digitalis CO was increased in 7 patients, reduced in one and essentially unchanged in the other 4. The average CO was increased from 4 03 to 4.37 L. per minute (p = NS). Since heart rate was not significantly altered by digitalis, changes in CO reflected changes primarily in stroke volume.

SVR in the later phase up to an hour after digitalis showed variable changes. SVR was higher than in the control period in 3 patients, lower in 3 and essentially unchanged in 6. The average SVR fell from 1 904 to 1 758 dynes-sec -cm $^{-5}$ (p = NS). The effect of digitalis on SVR showed an apparent relationship to control SVR. The two patients with the highest control SVR (7 659 and 4,2-6 dynes-sec.-cm $^{-5}$) exhibited sharp reductions 20 and 56 minutes after ouabain respectively. On the other hand 3 of the 7 patients with control SVR less than 1,500 dynes-sec -cm $^{-5}$ exhibited rises in SVR 30 minutes after administration of ouabain or deslanoside.

Since the dye sampling site varied in different patients from the left ventricle to the abdominal aorta absolute values for central blood volume (CBV) could not be compared. However the changes following digitalis in individual patients should reflect primarily changes in cardiac and pulmonary volume. CBV was increased by 40 and 150 ml. during the early pressor phase in the 2 patients studied. In the later phase CBV was decreased from control values by an average of 37 ml. (p = NS).

VENTRICULAR FUNCTION. The time course of changes in LV dp/dt and LV systolic pressure were plotted following seven infusions of ouabain in 6 patients (Fig. 3). Heart rate did not change in any of the subjects. At the time of the rise in systolic pressure within the first minute LV dp/dt was either only slightly increased or in one subject, lower than in the control period. Even in the patient with the most prominent early increase in LV dp/dt, the initial

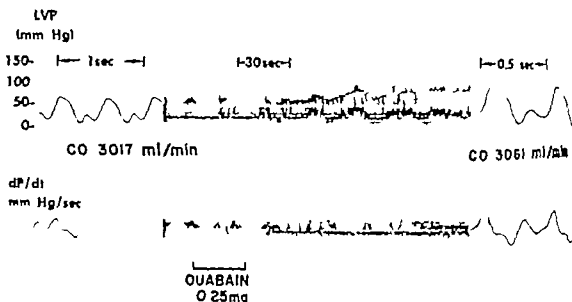


Fig 4 Recording I tient J W how that lthough left entricular pres ure and dp/dt rise sharply the first m t after of sion of ouabain rdiac output is not gnifica tly altered.

pressor effect was clearly not due to an increase in cardiac output (Fig 4) LV dp dt tended to rise gradually for 10 to 30 minutes after ouabain (Fig 3) but in 2 patients (L W and W B) a sharp fall in dp dt accompanied a precipitous increase in LVEDP at a time that LV systolic pressure remained elevated In one patient with pulmonary embolism (F W) right ventricular dp dt was monitored simultaneously with LV dp/dt RV dp/dt increased by 24 per cent and LV dp dt by 23 per cent following administration of 0 5 mg ouabain.

Left ventricular stroke work (LVSW) increased after digitalis from an average of 32 3 to 40.3 gmM (p < 0 01) In 10 of 12 subjects an increase in LVSW was accompanied by a reduction in RAP or LVEDP indicating a shift to the left of the myocardial function curve in the late phase (15 to 60 minutes) after digitalis administration Data were satisfactory for measurement of left ventricular ejection times (LVET) in 10 subjects. LVET decreased slightly but insignificantly following digitalis from an average of 0.226 to 0.223 sec. However the mean systolic ejection rate (MSER) increased in 9 of the 10 patients (Fig 5)

The tension time index (TTI) showed variable changes from control in the late phase but in the first 5 minutes after digitalis injection TTI was consistently increased (Fig 5)

CLINICAL RESPONSE *None of the patients* exhibited bedside evidence of dramatic improvement after digitalis, even when arterial pressure and cardiac output were moderately increased Specifically skin circulation was not obviously improved, urine output did not increase and cerebral signs did not clear

Two patients had adverse responses to ouabain as described above Patient L B developed pulmonary edema 5 minutes after injection of 0.25 mg Patient W B seemed to improve initially after a total dose of 0.5 mg but 15 minutes after the second 0.25 mg injection LVEDP rose abruptly to 25 mm Hg and LV dp dt fell Ventricular fibrillation ensued and resuscitation was unsuccessful.

The hemodynamic response to digitalis was similar regardless of the underlying cause of the cardiogenic shock. In patients with acute myocardial infarction CO was increased in 3 and unchanged in 2 similar to the results in patients with other nonspecific causes of cardiogenic shock. Myocardial performance as estimated by the cardiac function curve the LV dp/dt and the MSER improved after digitalis even in patients in whom cardiac failure was

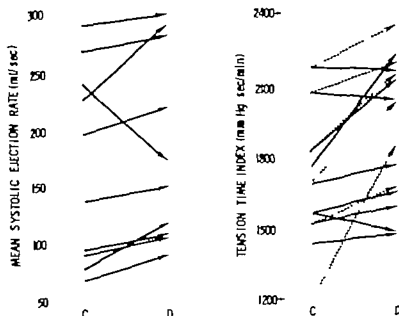


Fig. 5 Effect of digitalis (*D*) on left ventricular ejection rate and tension time index in patients with cardiogenic shock. Solid lines depict changes from control (*C*) during the late phase and the dotted lines changes during the early phase after digitalis administration.

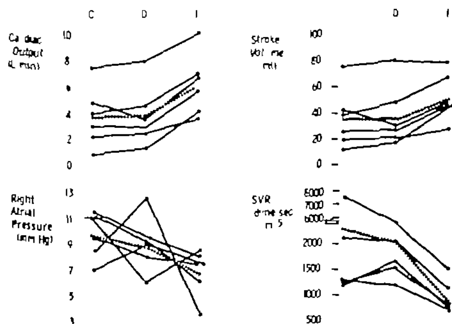


Fig. 6 Comparison between hemodynamic effects of digitalis (*D*) and isoproterenol (*I*) in 6 patients. *C* represents control observations. Broken lines show average changes for the group.

apparently a terminal manifestation of prolonged shock (Patients F R, A I, and H O).

COMPARISON WITH ISOPROTERENOL. Six of the patients also were given infusions of isoproterenol from 5 to 30 µg per minute. In 3 (J I, L I, and A I) isoproterenol was evaluated first. In these patients control observations for digitalis were performed at least 30 minutes after the isoproterenol infusion was discontinued. Direct comparison between the two agents in this group therefore is possible. In the other 3 patients (L W, F R, and H O) the isoproterenol was begun from 10 to 30 minutes after digitalis administration and the response therefore represents the additive effect of isoproterenol and digitalis.

In all 6 patients isoproterenol alone or isoproterenol plus digitalis resulted in a considerably higher CO than digitalis alone ($p < 0.05$) (Fig. 6). Although the heart rate during isoproterenol infusion averaged 10 beats per minute faster than after digitalis, SV was nonetheless higher during isoproterenol administration in 5 of the 6 subjects. SVR was not significantly altered after digitalis in these 6 subjects, but isoproterenol produced a sharp reduction in SVR in each patient from an average of 2,331 to 942 dynes-sec-cm^{-5} ($p < 0.01$).

RAP was slightly lower during isoproterenol infusion than after digitalis in 5 of the subjects, and LVEDP measured in 3 patients was much lower during isoproterenol infusion in one but slightly higher in the other 2. LV dp/dt was increased by an average of 35 per cent by digitalis but it rose an average of 72 per cent during isoproterenol infusion. However, the faster heart rate induced by isoproterenol makes direct comparison of changes in dp/dt as an index of inotropism unreliable.

The clinical response also was more dramatic during isoproterenol administration. The skin usually warmed considerably and the peripheral pulses became fuller. Sweating often subsided. Premature ventricular beats almost always occurred as the infusion rate of isoproterenol was increased. These promptly subsided as the dose was decreased and they were not troublesome if the intravenous drip was carefully monitored. The dose employed in these studies was usually the maximum infusion rate that could be tolerated without a dangerous change in rate or rhythm.

Discussion

Although the term cardiogenic shock has traditionally been reserved for the syndrome of shock following myocardial infarction, bedside hemodynamic studies have made it clear that impairment of cardiac function may be the principal cause of the circulatory deficiency in patients with shock of other etiologies as well.[12] Since treatment in all these patients must be directed toward improving myocardial performance, it seems appropriate to adopt a more physiologic definition of cardiogenic shock. Patients were included in the present study if peripheral signs of shock were accompanied by evidence of cardiac impairment based on measurements of right or left ventricular filling pressure and cardiac output. Five of these patients had sustained an acute myocardial infarction, but the other 8 suffered from a wide range of medical illnesses. Certain hemodynamic differences were apparent within the group. The patients with myocardial infarction generally had the most severely impaired cardiac function. Five of the other patients also exhibited low cardiac outputs, but in 3 the cardiac index was within the normal range. In these latter patients the CO apparently was inadequate to support the peripheral circulation, either because of a redistribution of blood flow or because this CO represented a considerable reduction from the patient's previous level. Since the CO in these 3 patients was maintained only by an elevated cardiac filling pressure, and since their response to digitalis was similar to that of the patients with low outputs, it was felt justified in pooling the data from all 13 patients.

The inotropic effect of digitalis has been amply demonstrated in isolated hearts, experimental animals, and patients with normal and diseased hearts.[1-4] In the present study several digitalis preparations were shown to have an inotropic effect in these patients with cardiogenic shock. An improvement in myocardial function with

one hour after intravenous administration of ouabain deslanoside or digoxin was manifested in each of the patients by one or more of the following (1) an increase in left ventricular stroke work associated with a fall in right atrial or left ventricular end diastolic pressure (a shift to the left of the Frank Starling curve)[4] (2) an increase in the maximum rate of rise (dp, dt) of right or left ventricular pressure[1] or (3) an increase in the mean left ventricular ejection rate[18]

Despite the apparent increase in myocardial contractility however cardiac output rose following digitalis by an average of only 0.34 L. per minute (8 per cent) Therefore peripheral blood flow usually was not significantly improved during the period of observation following administration of ouabain, deslanoside, or digoxin These results in patients with cardiogenic shock are similar to previous observations in normal subjects, who exhibit an inotropic effect following digitalis administration but no consistent change in cardiac output.[19-20]

It is possible that a greater rise in cardiac output might have been observed if larger doses of digitalis were given or if the observation period were longer Cardiac output was measured from 20 to 43 minutes after infusion of deslanoside or digoxin which have been shown by Weissler and his associates to produce an inotropic effect within 10 minutes after administration Furthermore 7 patients received ouabain, which has an even more rapid onset of action Although these patients probably did not receive the maximum tolerated doses of the glycosides, an inotropic effect of the drug was demonstrable in each patient, and supplementary doses administered therapeutically to 3 patients did not further improve myocardial function Therefore it is likely that the effects observed were representative of the acute therapeutic efficacy of digitalis in these patients

One of the most consistent effects of digitalis was a small but significant reduction in right atrial pressure. A similar response was observed in dogs by Cotten

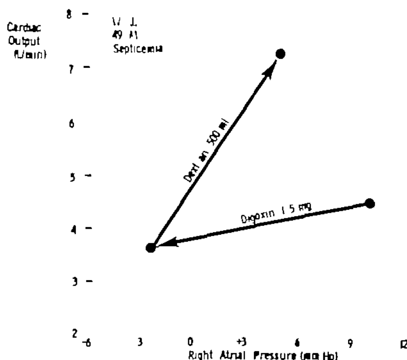


Fig 7 Changes in cardiac function in patient with septicemia and cardiogenic shock. Cardiac output fell after digoxin, but volume expansion then restored normal output with right atrial pressure lower than that prior to digoxin administration.

and Stopp[11] who demonstrated that if right atrial pressure was maintained constant after digitalis a prominent increase in cardiac output occurred. Fig. 7 depicts a clinical example of this phenomenon. This patient with septicemia was not included in Table 1 because dextran had been administered prior to digitalis therapy. Following injection of digoxin cardiac output and right atrial pressure were lower than after initial volume expansion. Infusion of another 500 ml of dextran at this time led to a sharp increase in cardiac output. Thus the improvement in myocardial function resulting from digitalis in the patients with cardiogenic shock in this series might have been translated into more dramatic increases in cardiac output if cardiac filling pressure had been maintained constant with volume expanders.

The fall in right atrial pressure after digitalis could be attributed to several possible mechanisms. In the absence of changes in myocardial compliance the reduction in pressure signifies a reduction in end-diastolic volume. Digitalis has been shown to exert a constrictor effect on the hepatic veins of dogs resulting in splanchnic pooling and a decreased venous return to the heart.[22] The same mechanism has been implicated by some authors to account for the beneficial clinical response to rapid digitalization in congestive heart failure.[8] However right atrial pressure did not fall during the first 5 minutes after administration of digitalis, when peripheral vascular effects were clearly present but only during the later phase when an inotropic effect had already occurred. Therefore it is unlikely that the decrease in cardiac volume was a mechanical consequence of vasoconstriction. A better explanation would be a gradual reduction in venous volume or an increase in the capacitance of the venous system. An increase in myocardial contractility could result in the transfer of some blood from the venous to the arterial system and lead to relaxation of venoconstrictor impulses and an increase in venous compliance.[23] On the other hand the rise in arterial pressure particularly if accompanied by venoconstriction might increase capillary hydrostatic pressure and result in a gradual fall in circulating plasma volume.[24] Thus, a fall in cardiac volume after digitalis could result from the interplay of a number of simultaneous hemodynamic events.

The most dramatic effect of all three digitalis preparations in these patients was a prompt rise in arterial pressure which was apparently due to peripheral vasoconstriction. A nonadrenergic arteriolar constrictor effect of digitalis has previously been demonstrated in animals[4,5,6] and in man.[1,24] Following the initial pressor phase total peripheral resistance remained increased in some patients in this series but fell to below control levels in others. It is likely that these later effects of digitalis on vascular tone represent the summation of opposing factors, as suggested by Mason and Braunwald.[25] These authors found an increase in forearm vascular resistance after administration of digitalis to normal subjects but in patients with congestive heart failure a fall in vascular resistance was attributed to relaxation of heightened sympathetic tone. Similar results were observed in the present study. Several of the patients with low initial total vascular resistance exhibited a sustained rise in systemic resistance after digitalis administration. On the other hand, the patients with high resistance and cutaneous vasoconstriction indicative of heightened adrenergic discharge usually responded to digitalis with a fall in systemic resistance as myocardial function improved.

The early peripheral vasoconstrictor effect of digitalis usually preceded the onset of a potent inotropic effect of the glycoside and was associated with an increase in left ventricular work and tension time index. LVEDP rose precipitously in several instances and one patient developed frank pulmonary edema, which has previously been reported as a complication of digitalization in congestive heart failure.[27] Acute heart failure was observed only with ouabain in this series; however left ventricular pressures were not measured after administration of the other drugs and a similar response therefore might have been missed. Indeed the early vasoconstrictor effect of digoxin and deslanoside probably precedes the inotropic effect by a considerable interval and the hazard of acute left ventricular failure might be greater after these drugs than

after ouabain. The most likely cause of the acute left ventricular failure is the increase in afterload and myocardial oxygen demand[illegible] in the presence of severe myocardial and/or coronary arterial disease. Since LV dp/dt fell sharply in 2 patients when LVEDP rose, it is possible that the left ventricle transiently entered a descending limb of its Starling curve or that myocardial hypoxia induced a further acute impairment of cardiac function. This untoward effect of digitalis is probably similar to the acute heart failure we have previously observed in patients with cardiogenic shock who were given angiotensin which also increases arterial pressure without much myocardial stimulation.[illegible] Other effects of digitalis could have contributed to the left ventricular failure. Coronary vasoconstriction might accompany the vasoconstrictor effect of digitalis[illegible] and could have aggravated myocardial hypoxia. Furthermore, mobilization of the sequestered splanchnic blood volume (which has been described by Ferrer and associates[illegible]) after administration of digoxin to patients with congestive heart failure could have acutely overloaded the central circulation. Although the dose response and temporal characteristics of the direct vascular actions of digitalis are not known, the relatively rapid infusion of the glycosides in these patients could have contributed to the prominent vasoconstrictor effect. It might thus be advisable to administer digitalis more slowly or to avoid the intravenous route in clinical situations where vasoconstriction is liable to be deleterious.

The importance of peripheral vasoconstriction in the overall hemodynamic response to digitalis is further exemplified by a comparison between the effects of digitalis and isoproterenol, a cardiac stimulating drug which induces peripheral vasodilation.[illegible] Arterial pressure was usually slightly lower during infusion of isoproterenol, but stroke volume, cardiac output, and left ventricular ejection rate were nearly always considerably higher regardless of whether the isoproterenol was given before or after digitalis administration. It cannot be established from this study if the greater cardiac output response to isoproterenol is related to a more powerful inotropic effect or to a reduction in afterload resulting from its peripheral vascular actions.

Decisions regarding the clinical usefulness of pharmacologic agents in cardiogenic shock must be based on additional considerations besides acute systemic hemodynamic responses. Although isoproterenol usually more effectively improves total blood flow than does digitalis, the regional distribution of this improved blood flow and the myocardial metabolic response to the inotropic and chronotropic effects of the isoproterenol must be considered. Indeed, therapy for cardiogenic shock should be highly individualized and the choice of drugs probably should be based on the individual's clinical and hemodynamic response. Thus, these data do not establish the relative efficacy of these inotropic agents in the management of the patient in shock. However, the results do make it clear that despite its inotropic effect digitalis should not be expected to furnish a dramatic improvement in blood flow in cardiogenic shock and its intravenous administration in certain patients may be hazardous.

Summary

The hemodynamic effects of cardiac glycosides were studied in 13 patients with cardiogenic shock. Intravenous administration of ouabain, deslanoside, or digoxin produced a prompt pressor effect which was characterized by increases in systemic vascular resistance and tension time index and no change or increase in right atrial pressure (RAP) and left ventricular end-diastolic pressure (LVEDP). Acute pulmonary edema developed during this period in one patient. During the later phase, 15 to 60 minutes after infusion of digitalis, there were increases in the maximum rate of rise of left ventricular pressure (LV dp/dt), mean systolic ejection rate, and left ventricular stroke work, usually with a fall in RAP or LVEDP. Despite the evidence of improved myocardial function, cardiac output (CO) was not significantly increased and was always lower than that attained during infusion of isoproterenol. It is concluded that digitalis is not very effective by itself in restoring blood flow in cardiogenic shock

and that the early peripheral vasocon strictor effect following intravenous ad ministration may be deleterious in some patients.

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Pulsatile aspects of coronary sinus blood flow in closed-chest dogs

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The recent development by some of us of a catheter tip electromagnetic flowmeter capable of measuring the instantaneous velocity of blood flow in small vessels enables one to study the pulsatile configuration of coronary sinus blood flow in closed-chest animals. This catheter flowmeter† consists of an electromagnetic flow transducer with signal sensing electrodes enclosed within a hollow flow-through cylinder at the tip of a cardiac catheter.

Most presentations of the pulsatile aspects of coronary sinus blood flow are based on early studies in open-chest dogs by Anrep and associates in 1927 and Johnson and Wiggers in 1937. Marked variability of the wave forms was described by these investigators. Observations of reversal of flow within the coronary sinus were noted on some occasions. The techniques available at that time did not permit studies of phasic coronary sinus blood flow in closed-chest animals. The extent to which an open-chest preparation contributed to these observations has not been determined. Therefore, this study on closed-chest dogs was undertaken.

Methods

The catheter flow transducer. The catheter tip flow transducer consists of an electromagnet in the form of a solenoid coil attached to a flexible cardiac catheter and in close proximity to signal electrodes enclosed with an epoxy cylinder (Fig. 1). When the catheter is positioned within the coronary sinus, blood flows through the end hole of the epoxy cylinder past the signal-sensing electrodes and out the side hole. A zero flow reference base line can be obtained by occluding the end hole at the tip of the catheter against the wall of the right atrium or coronary sinus. Sampling of blood from the region of the tip of the catheter was possible through a polyethylene tube‡ (outside diameter 1.5 mm.) attached to the side of the catheter flow transducer.

The epoxy cylinder about the electrodes

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†Biotronex Laboratory, Inc., Silver Spring, Md.
‡PE 100 polyethylene tubing, Clay Adams, Inc., New York.

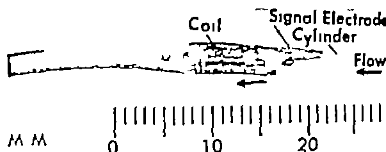


Fig 1 Photograph of tip of electromagnetic catheter flowmeter showing flow through cylinder signal sensing electrodes, and coil of the electromagnet

at the tip of the catheter serves the following useful functions (1) It prevents the wall of the blood vessel from interfering with the electrical field distribution in the region of the signal electrodes. (2) It provides a ready method for the determination of zero flow by means of occluding the end hole of the catheter against the side of a vessel or a cardiac chamber (3) It reduces the tendency to sense cardiac electrical activity

The epoxy cylindrical tip of the particular catheter flowmeter used for the flow velocities illustrated in this study was 7.5 mm long with an external diameter of 3.5 mm and an internal diameter of 3 mm at the tip The resistance of this particular tip was 1,400 dynes sec cm [5] The electromagnet and sensing electrodes were attached to a No 7 French size thin wall cardiac catheter The catheter tip flow transducer may be used with most electromagnetic flow systems. A Biotronex Laboratory Inc BI-610 was used in this study The catheter transducer has been shown to be linear throughout the ranges of flow that may occur in the circulatory system [1] The frequency response sensitivity and linearity of the electrical system are comparable to the performance of an external electromagnetic cuff transducer with a lumen of corresponding size Patterns of arterial flow measured with the catheter transducer in dogs were shown to be essentially identical to the patterns of flow obtained by cuff transducers surgically positioned about the vessels.[1]

Studies in closed-chest dogs Six healthy mongrel dogs of both sexes weighing 15 to 26 kilograms, were anesthetized either with methohexital sodium (Brevital) followed by chloralose (100 mg per kilogram) or with pentobarbital sodium (30 mg per kilogram) intubated and allowed to breathe room air spontaneously Intravenous injections of heparin (2.5 mg per kilogram) were given to all dogs prior to insertion of the catheter flow transducer and the dose was repeated every 30 to 60 minutes.

The catheter tip transducer was introduced through the right external jugular vein and the tip of the catheter was positioned in the coronary sinus with aid of a fluoroscope The location of the catheter within the coronary sinus was confirmed by measurement of the oxygen saturation of blood samples withdrawn from the coronary sinus. The position of the catheter within the coronary sinus was later verified by direct observation after opening the chest. Velocity measurements within the coronary sinus were made with the tip of the catheter 1 to 4 cm. from the ostium of the coronary sinus. Zero velocity base lines were recorded by pushing the tip of the catheter deep within the coronary sinus until the end hole of the catheter was occluded (Fig 2) The accuracy of this method for determining zero velocity was confirmed in open-chest dogs by palpating the tip of the catheter within the coronary sinus and manually occluding the end hole.

The catheter tip transducer was calibrated with the dog's own blood A gravity system connected to the epoxy cylinder was used and timed collections of blood were made with a stopwatch and graduated cylinder The output of the transducer was directly proportional to the volume of flow past the transducer The

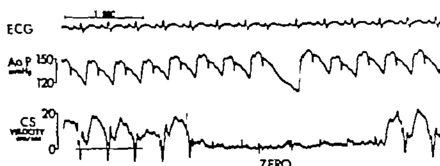


Fig 2 Simultaneous recording of coronary sinus (*CS*) blood velocity central aortic pressure (*A P*), and electrocardiogram (*ECG*) in the closed-chest dog Zero flow base line is shown. This was obtained by pushing the tip of the catheter far within the coronary sinus thereby occluding the flow through tip. I the velocity curve, an apparent presystolic reversal of flow was recorded.

velocity of flow past the transducer was calculated by dividing the volume of flow by the cross-sectional area of the lumen of the cylinder through which blood flowed

Central aortic pressure was measured with a Statham SF 1 catheter tip pressure transducer which was introduced through a carotid or femoral arterial cut-down and passed to the region of the aortic valve with the aid of a fluoroscope. The catheter tip transducer was calibrated after each pressure recording by means of a P23Db Statham transducer attached to the lumen of the same catheter In one dog a second 6 5 French size Statham SF 1 catheter tip pressure transducer was positioned in the coronary sinus. Pressures at these sites the electrocardiogram and the velocity of flow within the coronary sinus were recorded simultaneously on an Electronics for Medicine eight channel photographic recorder

Arterial blood oxygen saturation was measured in an American Optical oximeter to verify the adequacy of spontaneous respiration under anesthesia Saturation was 95 per cent or higher in all dogs included n this study

Following the completion of studies in the closed-chest animals, the thorax wa entered through a median sternotomy under artificial respirat on w th a Harv rd pump. The position of the t p of the cath eter transducer previously positioned with in the coronary sinus, was confirmed by palpation and inspection and measurements of coronary sinus velocity were repeated.

Results

Pulsatile flow patterns within the coronary sinus of closed-chest dogs showed considerable variation Such variations in contour were noted at different times in the same animal even when the tip of the catheter appeared to be in the same posi tion on the fluoroscope (Fig 3) Most of the coronary sinus flow in general oc curred during systole The onset of flow occurred during presystole (Fig 4) the isovolumic phase (Fig 3 *A* and *B*) or early ejection (Fig 3 *C* and *D*) Peak velocity of flow was reached during isovolumic contraction (Fig 4) the early ejection phase (Fig 3 *B*) the midejection phase (Fig 3 *C*) or the late ejection phase (Fig 3 *D*) On some occasions the ve locity of flow diminished promptly even during the early ejection phase (Figs. 3 *B* and 4) On other occasions, flow per sisted through all of systole and most of diastole (Fig 3 *A*) Minimal flow in general occurred during late diastole except in those cases in which there was a pre systol c onset of flow The variab lity of the configuration of coronary sinus flow veloc ty did not appear to depend upon the distance from the ostium of the coronary sinus at which velocities were recorded.

As would be expected from th shapes of the curves inscribed the percentage of flow that was systolic and the percentage that was diastolic showed marked vari ability Integrated systolic flow consti tuted 40 to 80 per cent of flow past the tip of the catheter The mean velocity of

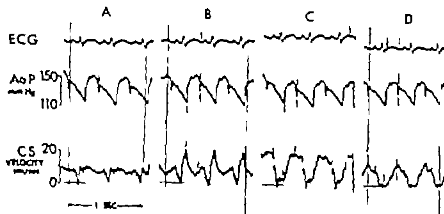


Fig 3 Simultaneous recordings of coronary sinus (*CS*) blood velocity, central aortic pressure (*AoP*), and the electrocardiogram (*ECG*) in the closed-chest dog. Time lines stand for 1 sec. Zero flow base lines are indicated. Vertical marks indicate the duration of the ejection phase. All tracings were recorded in the same dog with the tip of the flow catheter in approximately the same position within the coronary sinus. *A*, Onset of coronary sinus flow preceded ejection phase. Flow reached a plateau during systole and continued through most of diastole. *B*, Onset of coronary flow occurred during isovolumic contraction and reached a peak at end of ejection phase. Coronary sinus flow decreased during midejection but continued through most of diastole. *C*, Onset of flow occurred at start of ejection. Peak flow was reached during midejection and flow diminished during middiastole. *D*, Onset of coronary sinus flow occurred soon after the beginning of ejection. Peak flow was reached at the end of systole.

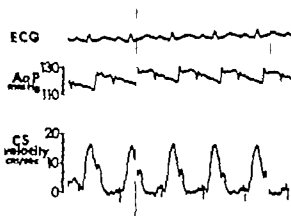


Fig 4 Simultaneous recording of coronary sinus (*CS*) blood velocity, central aortic pressure (*AoP*), and electrocardiogram (*ECG*) in the closed-chest dog. Time lines stand for 1 sec. Onset of coronary sinus flow occurred during presystole and peak coronary sinus flow was reached during isovolumic contraction. Coronary sinus velocity returned to zero levels during the ejection phase.

flow through the catheter tip ranged from 3 to 12 cm per second. The peak velocity of flow ranged from 8 to 28 cm per second. Considerable variation in the velocity of flow was observed at different times in the same animal even though the transducer was in approximately the same position.

In some cases a presystolic reversal of flow appeared to be present, but we could not convince ourselves of the validity of these observations (Fig 2). Whenever a reversal of flow seemed to occur, it was presystolic and in general constituted less than 1 per cent of forward flow. An apparent reversal of flow was shown less frequently in closed-chest dogs than in the same dog after the chest was opened.

Respiration often caused considerable beat-to-beat variation of coronary sinus velocity. The velocity of flow increased during inspiration and was somewhat out of phase with the respiratory variations in aortic pressure (Fig 5).

In one dog a catheter with a pressure transducer at the tip was positioned next to the catheter tip flow transducer within the coronary sinus. The tips of both catheters were within 1 or 2 mm of each other. Simultaneous recordings of pressure and the velocity of flow within the coronary sinus were made. Contrary to expectations, peak pressure within the coronary sinus was out of phase with peak velocity (Fig 6). Similar observations were made in an open-chest dog (Fig 7).

Variation of the configuration of coronary sinus blood velocity in dogs after thoracotomy was even more prominent

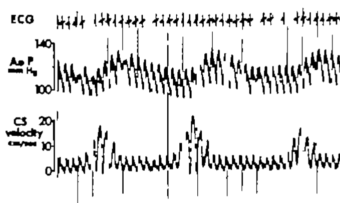


Fig. 5. Simultaneous recording of coronary sinus (*CS*) blood velocity, central aortic pressure (*A. P*), and electrocardiogram (*ECG*) in the closed-chest dog. Time lines stand for 1 sec. Phasic respiratory changes are noted in both *CS* velocity and aortic pressure. Maximum coronary sinus velocity occurred during inspiration. Cyclic changes of coronary sinus peak velocity are somewhat out of phase with changes of peak aortic pressure.

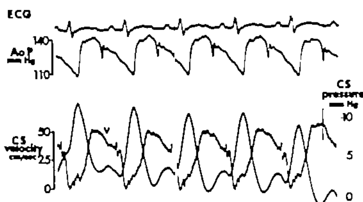


Fig. 6. Simultaneous recording of coronary sinus (*CS*) blood velocity, central aortic pressure (*A. P*), electrocardiogram (*ECG*), and coronary sinus pressure in the closed-chest dog. *CS* pressures in this illustration were recorded with a P23Db Statham transducer. This pressure recording system had a time delay of 0.07 sec. as compared to simultaneous recordings utilizing an SF 1 pressure-tip transducer in the coronary sinus. Peak levels of *CS* velocity flow (*V*) occurred out of phase with peak levels of coronary sinus pressure (*P*). The velocity of flow was greater than previously observed in the same dog (Fig. 5) in which recordings were made in the absence of a pressure catheter. The high flow velocities reflect an increased resistance due to the presence of two catheters within the coronary sinus. The extent to which this increased resistance affected the time relationship between pressure and the velocity of flow within the coronary sinus is uncertain.

than prior to thoracotomy. Manipulation of the heart frequently altered the pattern of pulsatile flow velocity within the coronary sinus.

Discussion

Measurement of the velocity of coronary sinus flow by means of a catheter with a flow transducer at the tip represents a readily feasible method for studying the velocity of flow within the coronary sinus of closed-chest animals. Electromagnetic flow transducers are ideal for the measurement of pulsatile flow because of their rapid frequency response and ability to sense directional flow. An electromagnetic catheter tip flowmeter for use in the coronary sinus was described by Lochner and Oswald. Their instrument utilized an occlusive balloon to direct all flow through

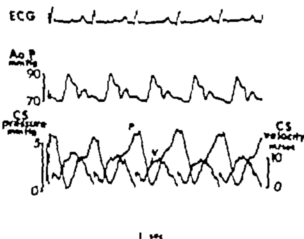


Fig. 7. Simultaneous recording of coronary sinus (CS) blood flow velocity, coronary sinus pressure, central aortic pressure (Ao P) and electrocardiogram (ECG) in the open-chest dog. Phase relationships between pressure and velocity of flow within the coronary sinus in this open-chest dog were similar to those shown in the closed-chest dog illustrated in Fig. 6.

the tip of the catheter. A single example of phasic coronary sinus flow was illustrated in their article in order to document the validity of the technique. Pulsatile aspects of coronary sinus flow were not studied.

Thermistor velocity probes have also been used for the measurement of coronary sinus velocity.[13] Casella and DeCaro[1] described such an instrument and it has subsequently been used in human subjects[11] including a patient during an episode of angina pectoris.[13] As is the case with all thermistors, this instrument suffers from an inability to sense directional changes. The frequency response of thermistor transducers is necessarily slower than electromagnetic transducers. Nevertheless illustrations were able to show pulsatile variation of coronary sinus velocity. These authors described respiratory variation of coronary sinus flow and seemed to show as we did that peak levels of coronary sinus pressure were not simultaneous with peak levels of coronary sinus *flow*.[13] A thermistor transducer was also utilized by Alfonso[13] for the measurement of coronary sinus velocity. Since his transducer had a slow frequency response (0.25 sec for 63 per cent of total deflection) phasic aspects of coronary sinus flow could not be measured with that instrument.

The velocity of flow measured within the coronary sinus of the dogs described in the present study suggests that the volume of flow was within the range expected for dogs. If one assumes that the coronary sinus was 5 mm in diameter and flow through the catheter tip was a representative sample the range of the mean velocity of flow (3 to 12 cm per second) would indicate a range of mean volume of flow of 28 to 110 ml per minute.*

The mechanism of the marked variability of the patterns of phasic flow velocity is not clear. Possible explanations include (1) variations of the mechanics of ventricular contraction and coronary sinus flow, (2) minor changes of location of the tip of the catheter within the coronary sinus, and (3) changes in orientation of the tip of the catheter within the coronary sinus due to motion of the heart. Neither variations of orientation nor variations of the location of the tip of the catheter within the coronary sinus would seem to explain these changes because variation of the pattern of phasic flow was noted in studies of open-chest dogs in which flow-measuring devices were sutured just at the orifice of the coronary sinus.[4,7] Obviously some artifact due to the methodology might be present. It is interesting to note that other investigators have reported a wide variety of patterns of *pressure* within the coronary sinus.[14] This suggests that the variety of patterns of flow recorded in the coronary sinus may be related to fluctuations of pressure.

As did Johnson and Wiggers,[7] we have seemed to record examples of reversal of flow within the coronary sinus, but could not be certain of the validity of these observations. Reversal of coronary sinus flow was not commented upon by Anrep and associates[4] because their methodology (a heat-sensitive flow device) precluded registration of directional changes.

An unexpected observation was the difference in phase between pressure and flow velocity recorded within the coronary

*The cross-sectional area of the No. 7 catheter to which the flow transducer was attached was subtracted from the measured cross-sectional area of the coronary sinus in these calculations.

sinus. It was necessary to insert two catheters within the coronary sinus to record pressure and the velocity of flow. Resistance due to the two catheters may have interfered somewhat with flow. This was apparent from the high coronary sinus velocity recorded with both catheters in place. Whether or not the observed phase differences were related to the increased resistance to flow caused by the catheters was not established. Similar phase differences between pressure and velocity of flow seemed to be shown in the recordings of Pellegrini and associates.[12]

This study demonstrates a new instrument for the investigation of blood flow within the coronary sinus. The method has been shown to be useful for physiologic studies in dogs. The catheter-tip flow transducer is now being modified by the addition of a soft flexible tip to permit its safe use in patients.

Summary

Phasic aspects of the velocity of coronary sinus blood flow were studied in closed-chest dogs by means of an electromagnetic flow measuring device located at the tip of a cardiac catheter. In agreement with observations in open-chest dogs, it was noted that flow was predominantly systolic and the wave form was characterized by marked variability. Peak flow velocity occurred at various phases of systole. Small presystolic reversals of coronary sinus flow seemed to occur occasionally in some dogs. Cyclic respiratory changes of coronary sinus blood velocity were not infrequently observed.

This study demonstrates a suitable method for the measurement of the velocity of flow within the coronary sinus of closed-chest animals, and perhaps, more importantly, demonstrates a method potentially applicable to human subjects.

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The effect of lignocaine on myocardial function, high energy phosphate stores, and oxygen consumption: A comparison with propranolol

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Recently Jewitt Kishon and Thomas[1] investigated the value of intravenous lignocaine (2-diethylamino-2 6 -aceto-xylidide) (Xylocaine) as an antiarrhythmic agent and concluded that it is the antiarrhythmic drug of choice in the management of ventricular arrhythmias after acute myocardial infarction The effectiveness of lignocaine as an antiarrhythmic agent in the treatment of ventricular arrhythmias and atrial ectopic beats which may occur after cardiac surgery and in the treatment of digitalis-induced arrhythmias is well established[2-4] Other investigators however have advocated that propranolol an adrenergic β receptor blocking drug should be used for this purpose[4-8] but this view should perhaps be modified by subsequent investigations[9-10] which have shown that propranolol impairs the ability of the left ventricle to perform mechanical work over a wide range of left atrial filling pressures and hence over a wide range of left ventricular end-diastolic fiber lengths. In addition propranolol has been shown to cause vasoconstriction in the coronary circulation[11]

As it had not been established that lignocaine is free from these undesirable effects the following experiments were carried out to determine the effect of lignocaine on myocardial function, high energy phosphate stores, oxygen consumption and coronary blood flow

Methods

Effect of lignocaine on myocardial contractions The direct effect of lignocaine on cardiac contractions was determined on either small papillary muscles excised from exsanguinated dogs or discarded from patients undergoing open-heart surgery especially for mitral valve replacement. The muscle preparations used were approximately 1.5 mm in diameter and were suspended isometrically in aerated (95 per cent O_2 and 5 per cent CO_2) modified Tyrode's solution[12] maintained at 37 ...

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American generic name, lidocaine.

0.5° C Stimulation was effected with suprathreshold rectangular pulses of 10 milliseconds duration delivered from a Tektronix square wave stimulator assembly at a rate of 38 pulses per minute. Preliminary experiments have shown that under the present experimental conditions high energy phosphate stores in strips of human and dog heart muscle are not significantly ($p > 0.5$) changed after 4 hours stimulation at this rate. Diastolic tension was adjusted until maximum tension developed during regular contractions. The contractions were detected with microsensor semiconductor strain gauges (type MS 132 120) arranged to form a wheatstone bridge the output from which was displayed on an ultraviolet light optical recorder (S E Laboratories, type 200S) Preparations were equilibrated in Tyrode's solution for 60 minutes before any drugs were added and the diastolic tension applied at the end of the equilibration period was maintained throughout the remainder of the experiment The tension developed during contraction was recorded continuously for 30 minutes before and for at least 60 minutes after lignocaine had been added to provide the required concentration. These apparently long periods of recording were used to ensure that any delayed action of the drug would not be missed

The Tyrode's solution was prepared in all-glass distilled water using Merck analytical reagent grade chemicals.

Effect of lignocaine on left ventricular function In previous studies dogs on right-sided cardiac bypass, in which inflow to the left ventricle and hence cardiac output is controlled have been used to determine the effect of various drugs, including *dl*-propranolol on ventricular function high energy phosphate stores, coronary blood flow and myocardial oxygen consumption In the present experiments this same technique has been used to determine the effect of lignocaine on ventricular function and to establish whether the effect of this drug on the heart is accompanied by a change in coronary blood flow myocardial oxygen consumption or in the level of high energy phosphate stores in the myocardium

Healthy mongrel dogs (12 to 16 Kg) were premedicated with 30 mg morphine sulfate given intramuscularly 1 hour before anesthesia was induced with 20 mg per kilogram sodium thiopental given intravenously An intermittent positive pressure respirator delivered oxygen to the dog through a cuffed endotracheal tube. Arterial blood pressure in the left femoral artery was detected by a Statham strain gauge transducer (P23Db) Left ventricular function curves were established and left ventricular work per minute (W) at a particular flow was calculated in gram-meters per minute, as previously described[1] as the product of total flow (Q milliliters per minute) multiplied by the pressure difference between the systemic arterial (P_{a}, in centimeters of H_2O) and left atrial pressures (P_{LA} in centimeters of H_2O) $W = Q \times (P_A - P_{LA})$ Although the term work is commonly used for this product, it is a measure of power i.e work per unit time.

In the control as in the experimental series, the output from the pump (and hence left atrial pressure) was increased in increments of approximately 10 ml per kilogram per minute As soon as stable conditions were established after each increment in flow mean atrial and arterial pressures were noted. The calculated left ventricular work per minute was plotted against left atrial pressure After a ventricular function curve had been established for each preparation and a ventricular biopsy taken (see below) to provide control observations, lignocaine was added intravenously either as a single bolus to provide a concentration within the range 0.2 to 5 mg per kilogram or as an infusion at a rate of 0 5 to 1 0 mg per kilogram per minute After lignocaine had been added as an infusion for 10 minutes or 10 to 20 minutes after it had been added as a single bolus both a left ventricular function curve and a ventricular biopsy were repeated These biopsy samples were analyzed for adenosine triphosphate (ATP) and creatine phosphate (CP) Throughout these experiments samples of arterial and coronary sinus blood were taken when required and their percentage oxyhemoglobin saturation estimated spectrophotometrically as previously described[11]

Biopsy technique and assay procedure for

high energy phosphates A description of the method used to ensure that the biopsy tissue was rapidly frozen has been described in detail elsewhere Briefly a small piece of muscle was drawn into a stainless steel tube which had been precooled with liquid nitrogen placed in close contact with the tissue Liquid nitrogen was then poured into the tube and the frozen biopsy tissue snipped off with a tonsil snare and immediately dropped into liquid nitrogen in which it was stored until analyzed usually on the same day Successive biopsies were taken from closely adjacent areas. Preliminary studies showed that the levels of ATP CP and IP in any one biopsy sample were not significantly ($p < 0.001$) different from the levels found in biopsies taken from closely adjacent areas.

ATP in a trichloracetic acid (TCA) extract of the biopsy was determined chromatographically as previously described CP was determined by the method of Furchgott and de Gubareff[12]

Statistical analysis The significance of results was determined by the Student t test taking $p = 0.05$ as the limit of significance

Drugs Dilutions were prepared in 0.9 per cent saline. Lignocaine was used as Xylocaine

Results

Effect of lignocaine on cardiac contractions The mean results of experiments designed to study the effect of lignocaine on the tension developed by isolated isometrically suspended strips of human and dog papillary muscle are summarized in Fig 1 where each point represents the mean ± S.E.M of six separate experiments. Cumulative doses of lignocaine were not used and the dose range studied was chosen to include the therapeutic range. In these experiments the negative inotropic effect of lignocaine was evident 2 or 3 minutes after it had been added to the Tyrode's solution in the organ bath and was fully developed within approximately 20 minutes. The data shown in Fig 1 relate to the fully developed response and show that the effect of lignocaine on the tension developed during contraction in dog muscle is not significantly different from that which occurs when human heart muscle is used Since these muscle preparations were stimulated to contract at a constant rate the depressant effect of lignocaine on cardiac contractions is not due to a change in the duration of the time interval separating successive contractions.

If after the negative inotropic effect of lignocaine was fully developed the Tyrode solution in the organ bath was replaced with lignocaine free solution, then the tension developed during subsequent contractions increased gradually until control conditions were re-established. Recovery was usually complete within 20 minutes. The negative inotropic effect of lignocaine on these electrically stimulated muscle strips was accompanied by a decline in the rate at which tension developed during individual contractions. For example, when the negative inotropic effect caused by adding 3 μg per milliliter of lignocaine was fully developed an additional 82 ± 12 msec.* (6 experiments) was required after the onset of contraction before the maximum or peak tension was developed in that contraction. This difference was significant ($p < 0.001$)

The negative inotropic effect of lignocaine on human and dog heart muscle is dose-dependent, as is shown by the data in Fig 1 and although the negative inotropic response caused by adding 1 μg per milliliter of lignocaine lacked significance ($p > 0.5$), the negative inotropic effect of doses of lignocaine of or in excess of 1.75 μg per milliliter was significant ($p = 0.01$)

Effect of lignocaine on left ventricular function high energy phosphate stores, coronary blood flow myocardial oxygen consumption and ventricular efficiency Previous studies have established that in control left ventricular work function studies increasing the output from the pump to provide small increments in left atrial filling pressure and hence in left ventricular end-diastolic fiber length results in comparatively large increments in left ventricular power so that when left atrial pressure is plotted against left ventricular work per minute the resultant curve has a steep slope.[11] In addition, these preliminary studies showed that successive

*Results presented as mean ± S.E.M.

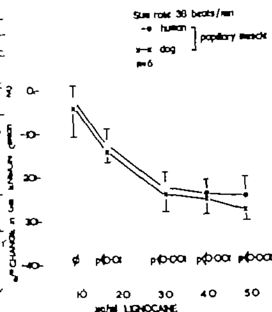


Fig. 1. Dose-response curve for the effect of 1.0 to 5.0 μg per milliliter of lignocaine on the tension produced by dog and human papillary muscle during isometric contraction. Per cent change in tension calculated $\frac{B-A}{B} \times \frac{100}{1}$ where B refers to tension produced before and A after the addition of lignocaine. Each point represents mean ± S.E.M. from 6 experiments. ϕ = not significant at level of p = 0.05.

curves established during 90 minute control perfusion do not differ significantly ($p > 0.5$) from one another and that the addition of 0.1 to 0.3 mg. per kilogram *dl*-propranolol to the perfusion system results in the curve being significantly flattened and displaced to the right. This effect of *dl*-propranolol on ventricular function was found to be accompanied by coronary vasoconstriction bradycardia and a diminution in the rate at which oxygen is extracted from the coronary circulation. Despite these changes in ventricular function the concentration of high energy phosphates stores in the myocardium remained unchanged.[13]

When in the present experiments, lignocaine was added either as a single bolus to provide a final concentration of from 0.2 to 4.0 mg. per kilogram or infused at rate of 0.5 to 1.0 mg. per kilogram per minute, left ventricular function over a range of left atrial filling pressures and hence over a range of left ventricular end diastolic fiber lengths, was not significantly different from that recorded from the same preparation before lignocaine was added. Left ventricular function curves recorded from a typical preparation before and 10 minutes after the addition of 1.0 and 5.0 mg. per kilogram lignocaine as a single bolus are shown in Fig. 2. Left ventricular work per minute performed by six other preparations at indicated left atrial pressures before and after adding lignocaine, either as a bolus or as an infusion as indicated, are listed in Table I.

The data in Table I relating to preparations Nos. 9 and 10 show that a dose of 5.0 mg. per kilogram lignocaine given as a single bolus did depress ventricular work per minute at the indicated left atrial filling pressure (4 cm. of H_2O) and the left ventricular function curve displayed in Fig. 2 shows that in contrast to the result obtained when the smaller dose of lignocaine was used a dose of 5.0 mg. per kilogram of lignocaine flattened the left ventricular work function curve particularly at higher left atrial filling pressures (6.5 to 10.5 cm. of H_2O) and displaced it to the right. Five other preparations yielded similar results. Other data listed in Table I show that the infusion of 0.2 to 1.0 mg. per kilogram per minute of lignocaine or the injection of 0. to 5.0 mg. per kilogram of lignocaine as a single bolus caused the heart rate to slow from a mean value (8 experiments) of 119 ± 9.6 to 108.5 ± 10.6 beats per minute. Although lignocaine reduced the heart rate coronary blood flow was maintained. Thus, in the 8 experiments listed in Table I the coronary blood flow before lignocaine was added was 16.25 ± 1.1 ml. per kilogram per minute. After adding either 2.0 to 5.0 mg. per kilogram of lignocaine as a single bolus or a ten minute infusion of 0. to 1.0 mg. per kilogram per minute of lignocaine the coronary blood flow in these same preparations was 16.75 ± 1.6 ml. per kilogram per minute. This difference was not significant. The conclusion that 0.2 to 5.0 mg. per kilogram of lignocaine does not cause any significant fall in coronary blood flow in these studies is supported by the data shown in Fig. *B* which indicates that coronary blood flow was maintained throughout the whole range of left ven

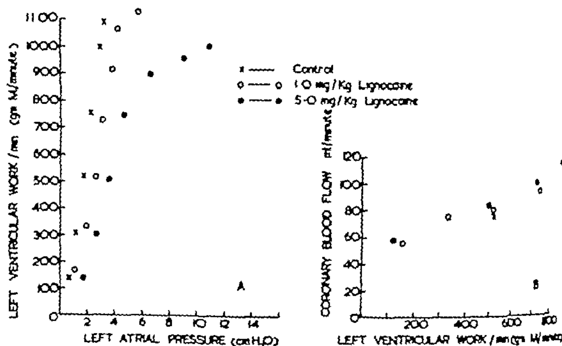


Fig 2 Effect of lignocaine on left entricular work/minute and coronary blood flow *A* Left ventricular function curve recorded f om typical preparation before nd after 1.0 and 3.0 mg per kilogram of lignocaine was added, as ndicated (prepar tion no. 13). *B* Relationship bet een left ventricular work per minute and coronary blood flow n typical preparation (no. 15) before and after adding either 1.0 and 3.0 mg per kilogram of lignocaine as indicated

*Table I Effect of lignocaine on ventricular function coronary blood flow and heart rate**

Dog	Lignocaine		Left atrial pressure (cm H_2O)	Left ventricular work/min (gm M /min)	Heart rate (beats/min)	Coronary blood flow (ml /Kg/min)
1	0 2 mg./kg /min	B	2	740	126	17
	(infusion)	A	2	750	108	15
2	2 0 mg /kg	B	2	790	156	21
	(single bolus)	A	2	800	156	17
4	1 0 mg /kg /min	B	2	860	152	16
	(infusion)	A	2	750	140	15
5	2 0 mg./kg	B	4	860	84	14
	(single bolus)	A	4	840	76	15
7	3 0 mg /kg	B	2	820	125	20
	(single bolus)	A	2	815	110	19
8	4 0	B	5	1,210	96	17
	(single bolus)	A	5	1 162	88	13
9	5 0	B	4	925	93	14
	(single bolus)	A	4	660	76	15
10	5 0	B	4	1 006	122	13
	(single bolus)	A	4	790	114	13
Mean ± S.E.M		B		901 4 ± 53 1	119 1 ± 9 6	16 2 ± 1 1
		A		820 9 ± 52 3	108 5 ± 10 6	16 3 ± 1 4
Sig				ϕ	ϕ	ϕ

*Where ϕ = not significant at level of p = 0 05, B refer to before and A after adding lignocaine at the indicated dose as either single bolus or an infusion. When given as an infusion, the infusion was maintained for 10 minutes before the ventricular function curve was re-established.

ricular function after either 1.0 or 5.0 mg. per kilogram lignocaine had been added as a single bolus to the circulation.

Myocardial oxygen consumption was determined for eight preparations before and after adding lignocaine and the results obtained summarized in Table II show that in these experiments the addition of this drug failed to cause any significant change in myocardial oxygen consumption. Before lignocaine was added the mean rate of myocardial oxygen consumption was 10.21 ± 1.59 compared with a rate of 11.20 ± 1.23 ml. per kilogram per minute (8 experiments) after adding lignocaine. This difference was not significant (p = 0.6).

When the ventricular efficiency index was calculated for these preparations, by dividing left ventricular work per minute (in gram-meters per minute) by left ventricular oxygen consumption (milliliters per minute), the results indicated that within the dose range studied lignocaine failed to cause any significant change (p > 0.01) in the efficiency with which left ventricular work was performed. In these eight preparations the efficiency index before lignocaine was added was 32.4 ± 1.1 compared with an efficiency of 32.2 ± 1.3 after the drug had been added. Analysis of the muscle biopsies for ATP and CP showed (Table II) that lignocaine

Table II. Effect of lignocaine on myocardial oxygen consumption, ventricular efficiency, and high energy phosphate stores

Dog no.	Dog weight (Kg.)	Lignocaine		Left atrial pressure (cm. H_2O)	Left ventricle work/min. (gm.M./min.)	Myocardial O_2 (ml./min./100 Gm. heart wt.)	Left ventricle O_2 (ml./min.)	Ventricular efficiency index†	ATP (µmole/Gm.)	CP (µmole/Gm.)
1	14.0	0.5 mg./Kg./min.	B	6	1,250	15.5	47.7	28.8	7.3	7.6
		(Infusion)	A	6	1,300	15.4	47.4	27.4	7.2	7.0
2	15.5	2.0 mg./Kg.	B	4	1,003	10.3	31.7	31.6	6.7	6.6
		(single bolus)	A	4	1,116	11.3	34.5	32.0	5.9	6.2
3	10.5	1.0 mg./Kg./min.	B	2	790	8.2	25.3	31.2	6.6	9.6
		(Infusion)	A	2	625	6.8	20.9	30.6	5.0	8.2
4	13.0	1.0 mg./Kg./min.	B	4	1,206	11.9	36.7	32.8	7.4	8.8
		(Infusion)	A	4	1,080	10.0	30.7	35.1	7.6	6.4
5	12.0	5.0 mg./Kg.	B	6	940	9.3	28.7	32.8	8.5	8.3
		(single bolus)	A	5	1,180	11.3	34.7	34.9	7.3	7.3
6	17.5	1.0 mg./Kg./min.	B	6	1,763	14.9	46.0	38.4	5.4	7.3
		(Infusion)	A	6	2,007	17.7	55.1	34.5	7.5	7.8
7	13.0	1.0 mg./Kg.	B	5	1,000	8.7	27.2	36.7	6.2	7.4
		(single bolus)	A	5	1,003	8.3	25.6	39.4	6.8	8.8
10	13.8	5.0 mg./Kg.	B	4	1,008	10.9	32.8	30.7	6.6	7.6
		(single bolus)	A	4	790	9.4	28.1	28.1	6.9	7.9
Mean ± S.E.M.			B		1,126.3 ± 100.1		32.4 ± 1.1	32.3 ± 1.1	6.9 ± 0.3	7.5 ± 0.4
			A		1,161.9 ± 66.2		32.2 ± 1.3	32.6 ± 1.5	6.8 ± 0.3	7.4 ± 0.3
Sig.					ϕ		ϕ	ϕ	ϕ	ϕ
					(p = 0.8)		(p = 0.8)	(p = 0.9)	(p = 0.9)	(p = 0.7)

*Where ϕ = not significant at level of p = 0.05. B refers to before and A after adding lignocaine at the indicated dose. Lignocaine was added either as a single bolus or infused at a constant rate as indicated. When given as an infusion the infusion was maintained for 10 minutes before the ventricular function curve was established.

†Ventricular efficiency index calculated

$$\frac{\text{L.V. work/minute (gm.M./min.)}}{\text{L.V. } O_2 \text{ consumption (ml./min.)}}$$

failed to cause any significant change in the myocardial stores of either ATP ($p > 0.9$) or CP ($p = 0.7$) in these preparations.

Discussion

These results show that lignocaine has a direct negative inotropic effect on dog and human heart muscle. This effect is accompanied by a decline in the rate at which tension is produced during individual contractions so that during each contraction a longer period of time is required for the development of peak tension. This negative inotropic effect of lignocaine which was significant only when the dose used exceeded 1 μg per milliliter cannot be accounted for in terms of a negative "staircase effect," since although lignocaine did cause the heart rate to slow in intact animals, the isolated papillary muscles were stimulated to contract at a constant rate. In this respect, then, lignocaine resembles propranolol. The negative inotropic effect of lignocaine on human heart muscle was not significantly ($p > 0.8$) different from that on dog heart muscle. Even when large doses of lignocaine were used, its effect on the left ventricular function was only apparent at the upper end of the curve under conditions of high load. Previous experiments have shown that propranolol depresses these left ventricular function curves even at the bottom of the function curve and hence under conditions of low load. In contrast to the results obtained when propranolol was used, the present results indicate that in the presence of lignocaine coronary blood flow was either maintained or slightly increased throughout the whole range of the minute work curve.

These results show that, within the dose range used, lignocaine failed to have any significant effect on the rate at which oxygen is extracted from the coronary circulation, a finding which again contrasts with results already described for propranolol.[8] These showed that propranolol depresses or has a "sparing" effect on the rate at which oxygen is extracted from the coronary circulation even though it impairs coronary blood flow throughout the entire range of the ventricular function curve. The rate at which oxygen was extracted from the coronary circulation in the present experiments is in approximate agreement with the control human data recently published by Dodge and Baxley.[9]

Like propranolol, lignocaine failed to cause any significant change in the concentration of high energy phosphates present in the myocardium so that, like propranolol, its negative inotropic effect cannot be explained in terms of a decrease in the availability of energy to support the process of contraction.

In general, these results are in agreement with those already described for lignocaine by Asokan and associates,[8] Schumacher and associates[14] and Constantino and co-workers[17] and may provide the basis for its relatively safe use[1-3] for the treatment of cardiac arrhythmias, in contrast to the well-documented dangers associated with the use of propranolol.[18,19]

Summary

The effect of lignocaine on the tension produced during isometric contraction by isolated dog and human papillary muscle, on ventricular function, on myocardial oxygen utilization and high energy phosphate stores, and on coronary blood flow was determined and compared with the effects already described for propranolol.

Doses of lignocaine of or in excess of 1 μg per milliliter decreased the tension produced during isometric contraction by isolated papillary muscle preparations and increased the time needed to reach "peak" tension during each contraction. Doses of lignocaine below 4 mg per kilogram or infusions of 0.5 to 1.0 mg of lignocaine per kilogram per minute did not cause any significant change in left ventricular function as determined by left ventricular work function studies. After 5 mg per kilogram of lignocaine was given as a single bolus, the work function curve was flattened at high but not significantly changed at low rates of work. High energy phosphate stores and myocardial oxygen consumption were not significantly modified when doses of lignocaine up to 5 mg per kilogram or infusions of lignocaine at a rate of 0.5 to 1.0 mg per kilogram per minute were used.

Lignocaine caused the heart rate to slow and reduced the resistance to blood flow in the coronary circulation. The efficiency

with which the left ventricle pumped blood into the circulation was not modified when lignocaine was given as a single injection or infused

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Computed ST forces of Frank and bipolar exercise electrocardiograms

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The possibility of earlier detection of potential coronary heart disease in healthy middle-aged persons was suggested by the more frequent observation of electrocardiographic ST segment depression after maximal rather than double Master two-step exercise. In addition, there was a provocative rise in age-specific prevalence of this response. All recordings were limited to a single bipolar precordial electrocardiogram (FCC) lead which was obliquely oriented in the horizontal plane of the chest (from the V_5 position in the precordium to inferior tip of the right scapula). Objective assessment of these ECG responses (even during exercise which introduced artifacts from skeletal muscle potentials, respiratory changes, and bodily movements) was achieved by ECG averaging and computer analysis.[1] Subsequent follow-up studies on one cohort of healthy men defined the sequential variability of ST response after maximal exercise over a 3 year period.[2] In 89 per cent the responses were constant, whereas in the remaining 11 per cent, responses changed. Unexpectedly, changes in responses were also associated with significant differences in risk factors of the subgroups, particularly resting blood pressure and serum lipid concentrations. Insofar as classification of individuals by criteria based upon a single ECG lead disregards information which may be present on mutually perpendicular lead axes, the question of more reliable classification by a more comprehensive ECG analysis remains unanswered. The positive relationship of bipolar ST responses to maximal exercise to coronary occlusive disease and collateral circulation in patients with chest pain syndromes have been described elsewhere.

This study reports the computer analysis and comparison of several portions of the ST segment recorded on the Frank lead electrocardiogram along with the bipolar lead previously used in ambulatory and individuals who exhibit either normal or abnormal responses to maximal exercise.

Methods

Thirty-nine multistage maximal exercise tolerance tests were conducted on 36 individuals (Tables I and II). The groups consisted of healthy persons and cardiac patients in the Cardiology Clinic of the University Hospital. Each subject walked until exhaustion on a motor-driven treadmill at speed and grade increased at 3 minute

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Table I. ECG analyses according to stages of standardized exercise test

Stage	Speed (m.p.h.)	Grade (%)	N*
Rest	0	0	39
Stage I	1.7	10	38
Stage II	2.5	12	37
Stage III	3.4	14	26
Stage IV	4.2	16	14
Stage V	5.0	18	0
Recovery			37
1 min. recovery			37
2 min. recovery			36
3 min. recovery			36
4 min. recovery			37
5 min. recovery			37

*Number of tests in which data were available (see text).

*Table II. Etiologic disease classification of subjects**

Etiology	ST abnormal (no. of patients)	ST normal (no. of patients)
Rheumatic valvular disease	3	4
Hypertension	1	1
Congenital heart disease	0	2
Coronary heart disease	3	6
Idiopathic myocardial hypertrophy	0	1
Heart disease of undetermined etiology	0	3
Normal	3	9
	10	26

*Patients included in this study represent consecutive cases for exercise testing in order to obtain unselected cases for study of ECG responses. The proportion of abnormal responses for any etiological category is not representative of that group. Furthermore, not all patients with angina and diffuse or multiple significant coronary vascular disease by arteriography exhibit significant ST depression after maximal exertion.

intervals. Patients who exhibited frequent ventricular premature beats, ventricular aneurysms, and/or right bundle branch block were excluded in order to avoid introducing distortions in the computer analysis of ST forces.

The usual CB ECG was visually monitored by continuous display on an oscilloscope, and by intermittent recordings each minute or oftener if indicated with an optimally damped properly calibrated direct-writing Sanborn 100 electrocardiograph (Model 100) with tested frequency response of 06-100 Hz. The Frank X, Y and Z orthogonal leads were recorded with a Hewlett Packard Vector Programmer Model 1507A, with high impedance buffer amplifiers for each lead. The bipolar lead and 3 orthogonal leads were recorded on a TMC (model 700-1400) pulse frequency modulated 7 channel magnetic tape recorder. Each ECG lead was transcribed on another channel with a constant time delay of 120 msec. to permit analysis of the PR segment for each heart beat which triggered the sweep circuit of the computer (TMC model 400B Computer of Average Transients) from the maximal downslope of the R wave. Since only 6 channels were available for signal recording (the seventh channel used for inverted signal to cancel flutter and wow from tape transport) transcriptions of the delayed Y and Z ECG leads were performed at recording site, while transcriptions of delayed bipolar and X leads were accomplished later on the initial Y and Z channels which were erased at the time of reading into the computer of average transients.

The Computer of Average Transients analyzed 100 beat samples of simultaneous CB bipolar X, Y and Z recordings taken at rest, at each stage of exercise and at minute intervals following exercise. The 400 computer addresses were divided into 4 groups; each had a duration of 0.625 msec. The sampling frequency for analogue to digital conversion was 1,600 Hz for a period of 250 msec. A differential trigger of the sweep circuit was triggered by the maximally negative dV/dt of the downslope of the R wave of the CB bipolar lead. The digitalized values were transferred to punched paper tapes which were analyzed by an IBM 1130 digital computer.

Using the X lead as a reference,† the

*See appendix for details.

†Mean voltages for ST, ST, ST, and ST located from the CB bipolar "fiducial" point were not significantly different (p > 0.05) from analogous temporal values located from the X fiducial point. Since this was true at rest, at Stage III of exercise, and at initial recovery after exercise, it was decided to use only the X "fiducial" point to locate the addresses of ST, ST, and ST.

computer located a fiducial point at the address corresponding to the nadir of the S wave. Specific areas of the ST segment were defined at addresses which were 30 to 39, 50 to 59, and 70 to 79 msec following this fiducial point. These were termed ST_1, ST_2, and ST_3, respectively. An average of ST_2 and ST_3 from 50 to 79 msec after the fiducial point was also defined as ST_A.[3] Magnitudes at each of these ST loci were related to an arbitrary zero reference located 20 to 39 msec prior to the nadir of Q in the QRS complex. Voltages (expressed in microvolts) were calibrated from the average deflection of 100 consecutive millivolt standardization signals recorded on magnetic tape. Once the addresses of ST_1, ST_2, and ST_3 were located on the X lead, the simultaneous addresses were located on the CB bipolar, Y, and Z leads.

Values for each of ST_1, ST_2, ST_3, and ST_A were calculated in the frontal, sagittal, and horizontal planes as follows (only ST_1 calculations shown):

$$ST_{frontal} = \sqrt{(ST_{1X})^2 + (ST_{1Y})^2}$$

$$ST_{sagittal} = \sqrt{(ST_{1Y})^2 + (ST_{1Z})^2}$$

$$ST_{horizontal} = \sqrt{(ST_{1X})^2 + (ST_{1Z})^2}$$

The spatial magnitude value for the ST vector in space was calculated for ST_1, ST_2, ST_3, and ST_A as follows:

$$ST_{spatial} = \sqrt{(ST_{1X})^2 + (ST_{1Y})^2 + (ST_{1Z})^2}$$

In accord with conventional practices, the X lead was defined as being positive when the electrical impulse moved toward the left. Y was positive when the electrical impulse moved downward. Z was positive when the electrical impulse moved backward.

In all 39 tests, the bipolar lead was examined visually at initial recovery and the ST forces were classified according to previously defined criteria. In 11 tests the response to exercise was classified as abnormal because of the presence of at least 1 mm (−0.1 mv.) ST segmental displacement below the PR reference voltage for 50 msec or more. The ST-abnormal group consisted of 10 men with an average age of 53 years. (Since not all cardiac patients, even those with clinical manifestations of angina pectoris or healed myocardial infarction, exhibit ST changes with exercise, classification according to independent clinical or hemodynamic criteria would dilute the evidence of ST changes after exertion demonstrated by part of the patients.) In the remaining 28 tests, the ST response was classified as normal because the ST displacement was less than 1 mm. The ST normal group consisted of 22 males and 4 females, with an average age of 42 years.

Mean computerized values for ST_1, ST_2, ST_3, and ST_A were calculated in the CB bipolar, X, Y, and Z leads for both the ST abnormal and ST normal groups for each period of observation. Calculations were made at rest, at all levels of exercise, and for the first 5 minutes of recovery. Intergroup comparisons for each variable were done by an unpaired Student t test.[4] Intergroup differences in frontal, sagittal, and horizontal plane vectors were also evaluated, as were the absolute spatial magnitude values of the ST vectors in both groups, for a total of 352 comparative t tests. Differences were not considered highly significant unless p values of less than 0.001 were achieved.

Quantitative data on ST forces in both normal subjects and cardiac patients were pooled together to define the relationship of the bipolar lead to the spatial representation by the Frank ECG at all loci and all periods of observation. Then a stepwise multiple regression analysis was performed on the ST_2 locus to define its proportional components in the Frank system. Finally, the relationship of the predicted bipolar ST_2 force (computed from the spatial data) to the observed bipolar ST forces was defined for the same and different case material. In the latter instance, quantitative ECG data from another 45 patients and normal subjects were employed.

Results

1. *Direction of ST vector changes.* During exercise, the ST vectors in both the ST abnormal and the ST normal group tended to move rightward, superiorly, and posteriorly. Hence, the ST segment tended to be depressed in the X, Y, and CB_5 bipolar leads, and to be elevated in the Z lead (Fig. 1). Immediately after exercise the

Table III *Frequency of computer differentiation ($p < .001$) of ST abnormal and ST normal groups before during and after exercise testing*

Differentiation by all 11 periods of observation

	Rest	I	II	III	IV	0	1	2	3	4	5	Total
No.	0	0	6	7	3	9	3	0	0	0	0	28 of 352 comparisons (8%)
% of all 32 combinations of 4 loci and 8 lead systems	0	0	18 8	21 9	9 4	28 2	9 4	0	0	0	0	

Differentiation by 4 ST locations at 5 relevant periods of observation in all 8 lead systems

	ST	ST	ST	ST_A	Total
No.	4	8	9	7	28 of 160 comparisons (17.5%)
% of all 88 combinations	4 5	9 1	10 2	8	
% of 20 combinations of 4 loci and 5 lead systems	20	40	45	40	

Differentiation by ST voltages in 8 ECG lead systems at 5 relevant periods

	CB	X	F	H	S	Y	Z	Spatial	Total
No.	14	11	2	1	0	0	0	0	28 of 40 comparisons (70%)
% of 20 combinations of 4 relevant lead systems at 5 periods of observation	70	55	10	5	0	0	0		

*For 4 ST loci, in 4 scalar 3 planar and 1 spatial ECG displays, for 11 periods of observation (4 8 11 = 352).

vectors reverted to an anterior location, resulting in ST depression in the Z lead.

2 *Frequency of computer differentiation of ST-abnormal and ST normal groups* Frequencies of computer differentiation of the ST-abnormal from the ST normal group are shown in Table III

PERIOD OF OBSERVATION At 11 periods of observation, 32 mean ST voltage measurements representing 4 ST locations in 8 leads were compared in the ST abnormal and ST-normal groups. The highest frequency of differentiation 9 of 32 values (28 per cent) was at initial (0) recovery and may reflect the fact that the original differentiation between the groups was made by visual inspection in this lead. The lower frequency of differentiation observed in Stage IV than in Stage III may be attributed to the small number of subjects who entered Stage IV (Table I) At the $p < .001$ level the computer was unable to distinguish between the 2 groups in any ST location in any lead at rest, Stage I or after 1 minute of recovery

ST LOCATION At each of 4 locations on the ST segment, 160 mean ST voltage measurements representing 8 leads during 5 relevant periods of observation were compared in the ST-positive and ST-normal groups. ST ST_3, and ST_A were useful in differentiating normal from abnormal responses twice as often as were the values of ST_1

LEAD SYSTEMS. For each of 8 lead systems, 20 mean ST voltage measurements repre-

Table IV. Voltage deflections for ST abnormal versus normal patients in relevant combinations of exercise or recovery lead and ST address (mean and standard deviation)*

Computer			Visual classification			
			ST abnormal		ST normal	
Treadmill stage	Lead	ST address	Mean	S.D. (n = 27)	Mean	S.D. (n = 11)
II	\	ST	− 127 ±	101	− 034 ±	039
II	\	ST	− 115 ±	108	− 012 ±	[illegible]
II	CB	ST	− 176 ±	146	− 039 ±	[illegible]
II	CB	ST	− 160 ±	154	− 023 ±	066
III	\	ST	− 146 ±	053	− 045 ±	[illegible]
III	\	ST	− 126 ±	060	− 012 ±	045
III	CB	ST	− 281 ±	088	− 108	[illegible]
III	CB	ST	− 248 ±	099	− 045 ±	[illegible]
0 Rec	\	ST_1	− 190 ±	223	− 018	[illegible]
0 Rec	\	ST	− 172 ±	245	− 021	054
0 Rec	CB	ST	− 215 ±	147	− 020 ±	[illegible]
0 Rec	CB	ST	− 181 ±	199	− 049 ±	[illegible]

*p < .001 for all comparisons.

senting 4 ST locations during 5 relevant periods of observation were compared in the ST-abnormal and ST normal groups.

Single leads. When the 4 leads were analyzed separately, the CB_5 bipolar lead provided differentiation between the 2 groups on 14 of 20 occasions (70 per cent). The \ lead was second in frequency and provided a criterion for differentiation on 11 of 20 occasions (55 per cent). The Y and Z leads were never useful in making the differentiation.

Combinations of leads. The frontal and horizontal coplanar lead combinations were only infrequently useful in differentiating between the 2 groups. The spatial magnitude of ST was only effective in making a differentiation at the p < 0.01 level of chance (rather than p < .001) occurrence at any stage of exercise using any portion of the ST segment.

3. *Magnitude of ST changes.* The digitized means and standard deviations for ST_1 and ST_3 and all relevant periods of observation are presented in Table IV. At all 3 periods of observation which are cited in this table, there were greater differences, in microvolts, between normal and abnormal responses observed with the bipolar lead [illegible] with the \ lead. Furthermore, in all in[illegible]stances, comparison of differences, in micro[illegible]volts, between mean values for ST_1 and [illegible] ST_3 revealed upsloping segmental displace[illegible]ment, that is to say, ST_1 was consistently less negative than ST_3, even in the abnor[illegible]mal group. Mean values for ST_1 locations for all 8 leads at all periods of observation in both ST-abnormal and ST normal groups are plotted in Fig. 1. Magnitudes of ST[illegible] were similar in Y and Z leads and in the [illegible] sagittal plane, whereas at high levels of work and early recovery the greatest dif[illegible]ferences (p < .001) were seen in the CB[illegible] bipolar lead.

Significance of differences in ST_1 voltage between the 2 groups were not due solely to magnitude. In the ST-abnormal group [illegible] large coefficients of variation[*] in ST_1 values during recovery are present in frontal horizontal and spatial vector leads. In the ST-abnormal group, the coefficient of variation in all leads but 2 tended to become much smaller as exercise increased.

*Coefficient of variation = $\frac{\text{standard deviation} \times 100}{\text{mean}}$

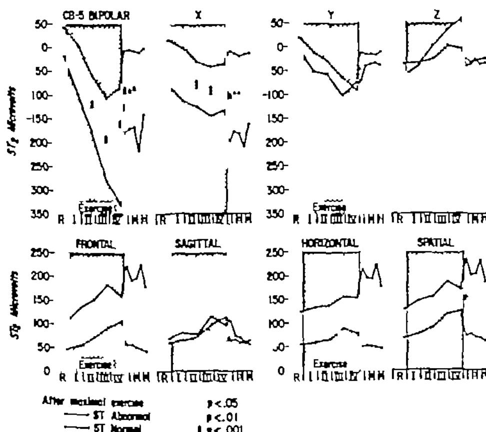


Fig 1 Comparison of ST mean voltages. Microvolt values of ST are show 0 level of rest exercise, and recovery for both the ST-abnormal and ST-normal groups. The groups are differentiated best by the CB₅ bipolar and X leads. Although mean values for ST are quite differen in frontal, horizontal, and spatial leads (all of hich ha e an X component) the variance of these means is too grea to produce ignificant difference (< .001).

4. *Internal checking* The 99 per cent confidence limits[4] for the ST normal group were calculated for the mean ST voltage at 0 recovery in the CB bipolar lead as well as in the X, Y Z and spatial magnitude leads. For the CB bipolar lead all 11 of the ST-positive tests fell outside the boundary set by the negative limit. For the X lead 10 of the 11 satisfied these conditions. However for the Y lead only 5 of the 11 ST-positive tests were more negative than the lower lim t of the 99 per cent confidence limit five fell with n the limits, and one was above the upper limit. In the Z lead 6 of the 11 ST al normal tests were above the upper l mit of normal 2 were w thin the normal range and 3 were below the lower lim t of normal. Inasmuch as ST becomes more positive in the Z lead during exercise e. moves more poste riorly but becomes negative i.e anterior at 0 recovery the differentiation of normal from abnormal is difficult to evaluate in this lead.

5 *Mul iva ate a lysis and predictability of b pola epola ization forces* Quanti tative data on all cases were combined in order to assess the relationship of the ST forces recorded n the bipolar lead w th the spatial transformation of ST forces recorded in the X Y and Z leads of the Frank lead ECG Regression analy ses of this relationship were made for ST ST ST_1, and ST forces fo each period of observation Correlation coeffic ents, presented n Table V revealed 3 points of interest (1) The highest oefficients of cor relation were obtained w th ST at rest and

Table V Correlations between spatial magnitude and bipolar magnitude of ST forces at [illegible] and 11 periods of observation

Period of observation	*ST*	*ST*	*ST*	*ST*
Rest	− 717	− 776	− 735	− [illegible]
Exercise				
Stage I	− 852	− 768	− 715	− [illegible]
Stage II	− 862	− 849	− 819	− [illegible]
Stage III	− 929	− 690	− 651	− [illegible]
Stage IV	− 547	− 488	− 394	− [illegible]
Recovery (min.)				
0	− 872	− 762	− 529	− [illegible]
1	− 858	− 876	− 143	− [illegible]
2	− 817	− 905	− 036	− [illegible]
3	− 810	− 943	− 290	− [illegible]
4	− 694	− 982	− 248	− [illegible]
5	− 953	− 955	− 240	− [illegible]
All period	− 838	− 858	− 517	− [illegible]

the last 5 minutes of recovery The highest correlation over all periods of observation was obtained with ST (2) Bipolar and spatial representations showed progressive loss of correlation as exercise loads increased from stages 2 to 4 Thus, the bipolar lead was not as representative of the spatial ST_2 forces recorded by the Frank leads during strenuous exertion even though it was quite representative before and after such exercise. (3) There was no correlation between bipolar and spatial representations of ST_2 forces during the first and second minutes of recovery This suggested that spatial forces, at this portion of the ST segment near the origin of the T waves, were essentially perpendicular to the axis of the bipolar forces. Furthermore some other independent phenomenon was occurring transiently during this phase of recovery Conceivably this represented the higher voltage T waves which have been associated with a transient hyperkalemia during this phase.[7]

Stepwise multiple regression analysis was performed to define the proportional components of the ST_2 forces. The bipolar ST force was considered the dependent variable while the 7 expressions of ST_2 forces in the Frank lead system (X Y Z frontal sagittal horizontal and spatial) obtained by appropriate transformations were taken as the independent variables. With only ST_2 the correlation coefficient was +0.9[illegible]. By stepwise addition of the remaining [illegible] independent variables, the multiple correlation increased to + 940 This indicated that as much as 88 per cent of the variance in ST_2 could be accounted for by the correlation of 7 expressions derived from the Frank lead system with the bipolar lead.

By utilizing the optimal regression formula the bipolar ST_2 voltages were predicted and compared with observed voltages recorded in several *other* patients to provide an external check of the "comparability" of the bipolar forces. The formula utilized data from each of the 3 Frank leads, the frontal plane and the spatial representation with the following equation

$$\textit{Predicted bipolar } ST_2 = 1\ 073\,(X_{ST_2}) + 366\,(Y_{ST_2}) - 619\,(Z_{ST_2}) + 420\,(\text{Frontal } ST_2) - 35\,(\text{Spatial ST}) - 008$$

Comparison of predicted versus observed bipolar ST_2 voltages in 226 comparisons after maximal exercise in 45 other patients showed a correlation coefficient of + [illegible]

*Whereas other independent variables, such as Taylor [illegible] might be used also, the logic of utilizing lead [illegible] common to the Frank electrocardiograms and the high correlation of 907 between X and bipolar leads hardly [illegible] this.

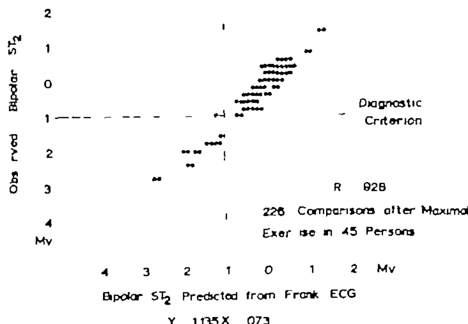


Fig. 2. Distribution of bipolar ST voltages after maximal exercise predicted from regression equation for Frank electrocardiogram and observed in bipolar CB lead. Open circles represent single observations and solid circles multiple observations (up to 13) plotted at same locations by computer program. Note high correlation and small numbers of false positives and false negatives in relation to arbitrary voltage criterion for abnormal response.

(86 per cent of the variance accounted for [Fig 2]) Dichotomizing the values according to the diagnostic criterion of an abnormal response, ≤ -1 mv 95 per cent were properly classified (chi square = 155 1 df $p < 0001$)

Two inferences are drawn from these observations. First, most of the information provided by the bipolar lead relative to ST changes following exercise is contained in the X lead of the Frank lead electrocardiogram. Second ST in the bipolar chest lead closely approximates the information content of the Frank system. Thus, the single bipolar chest lead provides a simple yet reliable clinical tool for assessing this portion of the ST segment changes induced by exercise.

Discussion

The above data indicate that the ST vectors move rightward superiorly and posteriorly during exercise Immediately after exercise they revert to an anterior location. Neither Frank X or Z scalar components, nor any of planar or spatial transformations differentiated the ST abnormal group from the ST normal group as frequently as the CB bipolar lead, which included projections from all 3 mutually perpendicular directions. Neither was the spatial magnitude ST_2, which includes all 3 scalar projections, as effective as the CB lead. It may be true that the major scalar changes during exercise are usually more or less parallel to the CB lead axis, which tends to accentuate these changes. Conversely excessive Y and Z information may minimize this differentiation. Nevertheless, for a patient with disease solely in the posterior myocardial wall, the Z lead might well identify ST vectors developing during exercise similarly for a patient with disease predominantly in the inferior wall the Y lead might be extremely useful.

Blackburn and associates concluded from a comprehensive analysis of over 40 lead systems or axes that if only a single lead is used for monitoring a lead with the reference electrode on the manubrium sterni and exploring electrodes at the chest position V_5 (CM_5) appears best, in all regards. Unfortunately the exact counterpart of the bipolar CB lead was not in-

cluded in their study and the limited number of channels for recording on magnetic tape precluded further analysis of that CM_5 lead in this study. Although an appreciable similarity between these leads might be inferred, a definite statement must await a direct comparison.

Other studies of the Frank lead exercise electrocardiogram have been reported by Blomqvist, Smith and Wherry, Ueda and colleagues and Isaacs and associates. Blomqvist utilized the same principle of averaging the ECG responses for a *variable* number of consecutive heart beats for 45 seconds of each period of observation. This adjusted for increasing the level of background noise as exercise increased the heart rate. The actual number of beats averaged increased from 20 at rest to 80 at maximal work. Rather than observe voltages at *fixed* time intervals from a "fiducial" reference in depolarization as in this study, Blomqvist defined the onset and termination of the entire ST-T phase of repolarization and subdivided this into 8 equal components which were labeled T_{1-8}. Thus duration of any one of these components diminished as the heart rate accelerated and the duration of electrical systole shortened. Utilizing this system in a comparative study of normal subjects, both older and younger age groups, and patients with angina pectoris who were studied at known fractions (30, 60, and 100 per cent) of maximal oxygen intake, Blomqvist concluded that averaging was a definite asset to the methodology and quantitative assessment of the ECG responses was greatly facilitated. Furthermore, the ECG responses during exercise contained more information than ECGs recorded after exercise. Middle-aged men showed greater changes at maximal loads than younger men. The maximal information for the differentiation of angina pectoris from normal men was located in the T segment or approximately the midpoint of ventricular repolarization from the end of QRS to the end of T. Linear discriminant functions achieved complete separation of patients from normal subjects at work load levels below and at the threshold of anginal pain. Variability with repeated testing of normal controls was relatively low, ± 7 per cent. An apparent difference between Blomqvist's data and the present study is the orientation of the ST forces on the Z axis during exercise. In this study the loops point more posteriorly with exertion, and revert promptly to anterior early in recovery after exertion. Although Blomqvist's mean values for the Z axis are anterior, there is appreciable variance in the Z value in both studies. Possibly this difference in Z axis values reflects a difference in patient sampling. Ueda and colleagues have noted that the exercise T vector may be directed anteriorly and leftward in patients with anteroseptal infarction, and posteriorly and leftward in those with anterolateral infarction.[11] Smith and Wherry,[11] as well as Isaacs and associates[12] also found significant differences in the midportion of repolarization, especially 3 minutes after exercise.[10]

The major difference with the present study is the location on the ST response curve in any lead for maximum differentiation between normal and abnormal responses. The optimal interval T_4 in the Blomqvist system occurs several milliseconds after the rigidly defined loci of ST_1 or ST_2. This raises a question as to which portion of repolarization should be most informative. From preliminary studies of hemodynamic recording of blood pressure with an optimally damped system, ST_1 appears to be related to the early portion of the aortic systolic pressure curve.[8] If so, appropriate ECG analysis may be more effective with a relatively fixed time of sampling and analysis, rather than an arbitrary fraction of the electrical systole whatever the heart rate. The specificity of the ST_2 criteria must await long term follow-up studies defining the subsequent course and life expectancy of these individuals.

It is concluded that although more comprehensive appraisal of early repolarization changes associated with exertional myocardial ischemia may be obtained with the Frank lead electrocardiogram, reliable classification of patients can be achieved from a single bipolar (CB_5) lead.

Summary

1. Simultaneous CB_5 bipolar and Frank X, Y, and Z orthogonal ECG leads were recorded during a standardized exercise test on 36 ambulatory individuals. From analysis of direct writing the CB_5 bipolar lead of

the moment of cessation of exercise 11 were classified by visual interpretation with an abnormal ST response and 28 with a normal ST response to maximally tolerated exercise. An objective computer method confirmed these subjective clinical differentiations. Classification of responses from X, Y and Z orthogonal leads was not more reliable than that from the CB bipolar lead

2. Multivariate analysis of normal and abnormal ECG responses grouped together showed the highest correlation between spatial and bipolar ST forces at the ST locus at rest and during most of the recovery and at ST_1 locus during strenuous exercise and immediate recovery During the second and third minute of recovery there was no correlation between spatial and bipolar ST forces.

3 Most of the ST information related to the bipolar lead was located in the X lead of the Frank lead electrocardiogram A satisfactory correlation between observed bipolar ST_1 and predicted bipolar ST forces (computed from X, Y Z frontal, and spatial measurements of the Frank lead ECG) was obtained by external checking in other patients.

4 A single bipolar precordial lead appears to be as reliable for purposes of classifying ECG responses to maximal exercise as the more comprehensive Frank lead system

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Appendix

1 *I a iance analys s of PQRST complexes* Using a Variance Computer with a Computer of Average Transients (CAT) the stabil ty of averaged QRS data was demonstrated In the a eraging mode the Variance Computer time multiplexed the incoming analogue electrocardiographic data and added the square of the signal as well as the signal to the CAT (Because the Variance Computer utilized one half the storage capacity of the CAT for averaging and the first 8 of these 200 addresses for cal bration voltages, only 192 ordinates of 1.25 msec duration were available for averaging and the total time for sampling was restricted to 240 msec.) During the computer mode of the Variance Computer the data in the CAT was recombined in the Variance Computer according to the variance equation

$$\frac{\text{sum of squares}}{\text{sample size}} - \frac{\text{square of sums}}{\text{sample size}^2}$$

Digital read-out of average and sum of

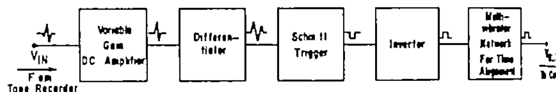


Fig 3 Differential trigger network.

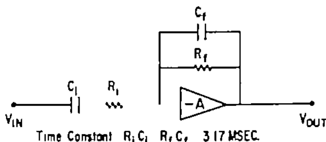


Fig 4 Differentiator

squares, along with additional computer programming provided variance in square millivolts.

2 *Excessive variance of original method* Consecutive read-out on an XY plotter of averaged PQRST complexes and associated variances revealed excessive variance in the qR region which made this a poor choice for triggering

3 *Description of revised differential trigger* Besides exhibiting greater stability the RS region represented the maximum rate of change in voltage and a more appropriate site for a triggering network utilizing the time derivative. A single-stop differentiator reduced the variance (in QRS sampling) since it utilized the maximum negative wave from the downslope of R. Therefore the revised differential triggering network (Fig 3) utilized the most nearly invariant point of the electrocardiogram as a time reference in averaging data. Pragmatically it was noted that the differential trigger worked more consistently than the amplitude-dependent trigger which utilized the qR portion of the cardiogram.

The original differentiator design was modified to attenuate high frequency noise (Fig 4) by proper selection of resistors and capacitors, it rolled off frequencies of 50 Hz or greater at −6 db per octave. This triggering network was virtually impervious to base line voltage shifts from bodily movements.

It was necessary to time-shift the pulse formed by the RS portion of the wave form to average the selected portion of the electrocardiogram (Fig 3) At 15 inches per second of the operational speed of the T[illegible] tape transport the instrument delay of [illegible] msec. was reduced to 120 msec by a potentiometer control in the one-shot multivibrator At the tape speed of 3¾ inches per second the fourfold longer delay was reduced to 120 msec. by the proper settings of potentiometers in a series of 3 multivibrators. The frequency responses of the tape recorder ranged from 0 to 2,500 Hz for the faster tape speed (15 in per second) to 0 to 625 Hz for the slower tape speed. The frequency response of the Sanborn Model 100 electrocardiographic machine was as low as 0 06 Hz (tested) to 100 Hz.

4 *Statistical effects of differential triggering* Two quantitative differences in wave form were found in 100 beat samples derived from a total of 39 periods of observation at rest exercise and recovery in [illegible] subjects whose electrocardiographic responses had been recorded on magnetic tape previously The interval from the nadir of Q to the nadir of S shortened by 2[illegible] msec. ($p < .01$) and the depth of S wa[illegible]

*Single-stop refers to differentiator whose response levels off at the corner frequency

increased by 0.05 mv ($p < .01$). Loci for ST segments have the effect on comparison with data from the original trigger method of being advanced approximately 1 msec. in time (the magnitude of the apparent RS shortening). Similarly, the PQ reference isoelectric voltage segment would be delayed 1 msec. in time (the magnitude of the apparent QR shortening). The ST forces observed at ST_1, ST_2, and ST_A loci were depressed by another 0.02 mv ($p < .05$) as compared with those of the original method. There was no difference in the magnitude of the standard deviations for the PQ and specified ST reference voltages derived by the different triggering systems. Nevertheless, the average dimensions of QRS and ST forces were altered slightly, presumably in the direction of more accurate representation of true values.

Because of the change in location of triggering from the upslope of R to its differentiated downslope (plus the modified time delay with a TMC recorder), the sampled data were effectively shifted in time, with a smaller portion of preceding PR components and a longer duration of ST-T components. This did not alter the specified sampling sites of the averaged voltages used for the PR reference voltages, which were set to zero voltage, nor the ST_1, ST_2, ST_3 and ST_A loci of the ST segment, which were corrected for that zero reference.

5. *Criteria for an optimal sample.* Statistical analyses of grouped data on 27 comparisons of 100 beat versus 16 beat samples of consecutive QRS-T forces by the differential triggering system showed less variance and significantly lower standard deviations by approximately 0.01 mv for both PQ and ST forces when the larger sample size (100 beats) was utilized ($p < .01$). Except for the S wave, which tended to be 0.04 mv deeper ($p < .05$), the sample size had no consistent effect on the dimensions of the QRS and ST forces. Whereas averaged values would be similar with a smaller sample (16 beats), larger variances would necessitate greater differences between comparable values for any 2 individuals before they could be differentiated reliably. Thus, the quantitative sensitivity of the method was compromised by use of 16 beat samples.

Morphologic and pathologic aspects of intercalated disc of the heart

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There are numerous reports in the literature of pathologic changes in the heart produced by many conditions. Most of these studies, however, are concerned with cellular alterations of the myocardium, whereas little attention has been paid to the intercellular junctional region, i.e., the intercalated disc. Electrophysiologic experiments suggest that the intercalated disc is involved with the electrotonic coupling between the interiors of adjacent cells.[3] The purpose of this report is to describe morphologic and pathologic aspects of the intercalated disc and also to discuss the possible functional role of the intercalated disc in the propagation of the excitation impulse.

Morphologic features

Laterally, the myofiber is bounded by a sarcolemma, which consists of an inner dense plasma membrane and an outer amorphous layer which, in its morphologic features, resembles the basement membrane of the surface epithelia (Fig. 1). Thus this layer is designated here as *basement membrane*. The basement membrane is separated from the plasma membrane by a clear area approximately 150 Å in width. At intervals the plasma membrane invaginates into the sarcoplasm, dividing the myofiber into cellular units, or myocytes. The transverse junctions thus formed at the intercellular boundary are known as intercalated discs. In light microscopy the intercalated discs appear as darkly stained bands. However, electron microscopic studies have greatly elucidated the details of the intercellular structural relationships of the cardiac myocytes.[illegible]

The intercalated disc traverses the myofibrils at the level of Z bands, usually at different levels in adjacent myofibrils, which gives the intercalated disc a steplike appearance (Fig. 2). The disc is differentiated into four three-dimensionally identifiable regions without any particular sequential order as to their location (Figs. 2 and 3). These regions have been variously designated as follows: (1) macula adherens or desmosome, (2) macula occludens, or tight junction—a quintuple-layered membrane junction, (3) fascia adherens or intermediate junction—the area of myofibrillar insertion, (4) nonspecialized region or normal intercellular gap region.

There are no quantitative studies available on the distribution of these differentiated areas.

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Fig 1 Longitudinal section of the myocardium of normal mouse. Sarcolemma consists of an outer basement membrane (*BM*) and an inner plasma membrane (*PM*). Various regions of the intercalated disc are identified. Note the presence of fibrillar cytoplasm in the myofibrillar insertion region (*MI*), and dense plate in the desmosome (*D*) region A small vesicle (arrow) is seen in continuity with the nonspecialized region (*G*). Nexal region (*N*) lies parallel with the myofibrils. (× 46,500.)

Macula adherens or desmosome The desmosomes can be easily identified by the presence of a dense plate about 200 Å in thickness subjacent to the cell membrane (Figs. 1 and 4) The cell membranes of the desmosome are parallel to each other and are separated by approximately 200 Å of intercellular space of rather uniform width In osmium-fixed myocardium the intercellular space is bisected by a thin intermediate membrane. Quite often the desmosomes are located between the regions of myofibrillar insertion suggesting that they may function as a device for strengthening the intercellular cohesion in the myofibrillar insertion region.

Macula occludens or nexus The nexus is the narrowest region of the intercalated disc, with a total width of about 125 to 170 Å The opposing cell membranes lie parallel to each other It is thought that the outer layers of two triple layered plasma membranes come into close contact to produce the quintuple-layered membrane junction the nexus (Fig 5) The central region of these five layers may appear as a slender membrane or a cribriform plate with perforations oriented about 90 Å apart The tight junctions or nexal regions of various tissues do not seem to be identical A considerable degree of structural variation has been reported [11-13] Similarly there is considerable variation in the structural stability of the nexus. In mammalian cardiac tissue the morphology of the nexus is quite stable and uniform even after severe mechanical and chemical treatment [14] Using the inorganic tracer lanthanum Revel[15] recognized two types of intercellular junctions in the broad category of tight junctions. The occluding junctions in the epithelia are truly tight junctions since they act as an impenetrable barrier to the passage of the small lanthanum particles. However the macula occludens or nexus of the intercalated disc in the mouse is not a comparable tight junction According to Revel the outer leaflets of the opposed cell membranes in the nexal area do not fuse. He described a 20 Å wide gap between the cells. The nexus in the intercalated disc of the mouse did not present a barrier to the passage of lanthanum particles.

Fascia adherens or myofibrilla insertion region This is a region of maximal interdigitation of the adjacent cells. The fascia adherens lies essentially transverse to the myofibrils and is readily identified by the presence of dense, somewhat filamentous material subjacent to the cell membranes (Figs. 1 and 2) The I-band filaments of the end sarcomeres of the myocardial cell are inserted into the condensed fibrillar cytoplasm associated with the fascia adherens During contraction the fascia adherens is probably the region of maximal tension The intercellular space in this region is about 200 Å wide.

Nonspecialized or normal intercellular gap region The intercellular space in this region is variable in width (usually greater than 200 Å) There is no particular structural specialization The cell membranes

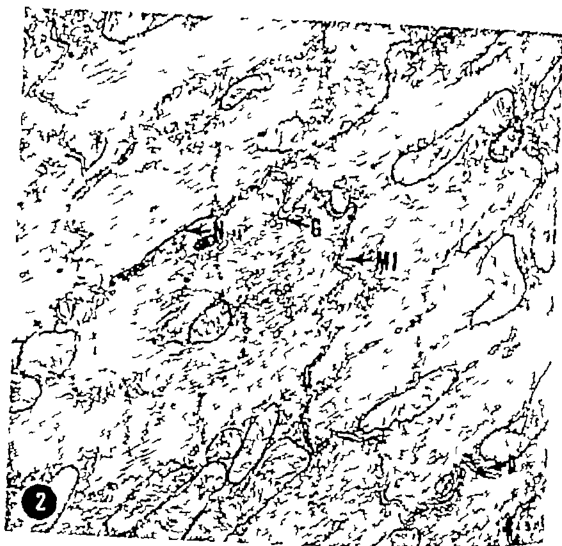


Fig 2 Longitudinal section of myocardium of normal mouse containing the intercalated disc which follows a step-like path and which is differentiated into desmosome (*D*), nexus (*N*), myofibrillar insertion region (*MI*) and a nondifferentiated region (*G*) (× 30 000)

from the adjacent cells follow an irregular plane. Occasionally vesicular structures in continuity with the cell membranes of this region are seen (Fig 1) These structures are probably a part of the sarcoplasmic reticulum.[14]

Experimental findings

Perfusion experiments with ferrocyanide,[3] ferritin[6,18] and lanthanum[22] indicate that the intercellular space of the intercalated disc is in direct communication with the extracellular space.

Propagation of excitation impulse at intercalated disc Until recently the heart was regarded as a morphologic syncytium. The syncytial hypothesis explained the myogenic transmission of the cardiac impulse. Electron microscopic studies have revealed without any reasonable doubt that the heart is divided into distinct and separate cells by the intercalated discs at their transverse junctions. It is necessary therefore to correlate the myogenic transmission of the heart with the cellular state of the heart. The intercalated disc also forms a physiologic barrier between the adjacent cells, as indicated by the arrest at the intercalated disc of microinjections of saline in the cardiac muscle.[4] The arrest of glycogen movement at the disc has also been described.[11,12] Furthermore, patholog

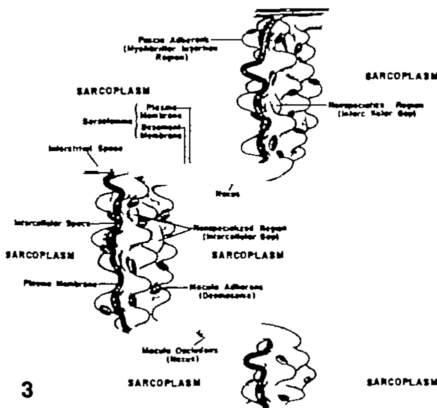


Fig. 3. Idealized three-dimensional diagram of normal mammalian intercalated disc.

changes may be strikingly different on the two sides of the intercalated disc.[39,40,42] There is some controversy as to the electrical resistance of the intercalated disc. Some authors believe that the intercalated disc is a region of high electrical resistance and that there are no low resistance pathways between the myocardial cells,[43-33] whereas observations of other authors indicate that the intercalated disc is a region of low electrical resistance.[4,34-46] If the intercalated disc is an area of low electrical resistance, the function of transmission of impulse should be related to the morphologic characteristics of the intercalated disc. Several authors contend that the nexus is the region of lowest electrical resistance allowing relatively unimpeded current flow between interiors of adjacent cells.[7,8,14] In a combined morphophysiologic study of frog atrial muscle, Barr and associates[4] reported that both the size of the nexal area and electrotonic coupling are reduced by hypertonic sucrose solution whereas a hypotonic sucrose solution increases both the size of the nexal area and the electrotonic coupling. However the evidence in support of these contentions is not convincing. In fact, even the existence of the nexus in frog heart muscle is questionable. The nexal areas in the frog heart muscle are either sparsely distributed or absent.[14] From the published electron micrographs[4] we could not detect any region where nexi were separated nor did the investigators point out the areas of nexal separation in the published micrographs, e.g. by labelling. Dreifuss and associates[9] found the intercalated disc disrupted except in the nexal area of rat ventricular muscle perfused with hypertonic solutions low in calcium concentration. However the propagation velocity of the excitation impulse was not reduced in such preparations. These investigators concluded therefore that the tight junction or nexus represents a low resistance electric pathway. In this regard the experiments of Muir[15] on the rat



Fig 4 Desmosome (*D*) of the myocardium of mouse at higher magnification Note a dense plate (arrow) on either side of the cell membrane in this region. (× 90,000)

heart perfused with calcium free solutions indicated that prolonged calcium deprivation produced an irreversible cessation of propagation of the impulse of excitation However Muir did not find any conclusive morphologic evidence of the nexal disruption in his preparations.

Failure to find the nexal area in the intercalated disc of many cold-blooded animals[1,36,41] which have similar electrophysiologic properties[7,38] further raises doubts as to universality of the nexus in electrotonic intercellular transmission It is also possible that the nexus may be created or destroyed by the preparatory procedures.[34,42] Further more tight junctions observed in some tissues, e.g. bean root mitochondria, do not seem to constitute low electrical resistance intercellular pathways. With the present state of our knowledge the nexal areas or tight junctions wherever they occur cannot be taken as *a priori* evidence for low resistance electric transmission.

As Rosenbluth[23] has pointed out, there are questions about the necessity of tight junctions at the sites of electric transmission Recently Revel[22] has observed a hexagonal array of subunits in the nexal region of the intercalated disc, which are similar to those observed by Robertson in electric synapses in nerve junctions. Whether or not these structures represent intercellular channels of ionic continuity remains pure conjecture Briefly it can be stated that there is as yet no satisfactory correlation between the physiologic evidence that the heart is a functional syncytium and the morphologic evidence that the heart is divided into discreet cellular units.

Pathologic changes of the intercalated disc. Recently Kawamura and Konishi[19] have advanced the concept of disease of the intercalated disc Widening of the intercellular space at the intercalated disc has been reported under various experimental conditions, e.g. phosphorous poisoning, inadequate nutrition[31] and potassium citrate administration[33] Poche[34] also reported the widening of the intercalated disc in the atrial appendage of a patient with valvular heart disease.

In our own studies, we have observed widening of the intercellular space in various experimental conditions. For example in rats exposed to prolonged periods of swimming (150 to 490 hours) dilation of the nonspecialized region of the intercalated disc was observed (Fig 6) In control animals the maximal width of the intercellular space in this region was about 0 1 μ, whereas in the hearts of exercised rats the maximal dimension of this area was 0 5 μ In rats which swam approximately 1,550 hours (for exercise protocol see reference 1) the intercellular space in the region of myofibrillar insertion was also dilated (Fig 7) In these animals some intercalated discs were separated from the sarcoplasm by an electron-lucent area (Fig



Fig 5 Nexal region (V) of intercalated disc of the m ocard m of mouse at higher magnification. The cell membrane in the adjacent region is trilammated (arrow) I the next region the outer leaflets of opposing cell membranes fuse to form 6 layered structure (X 53 000)

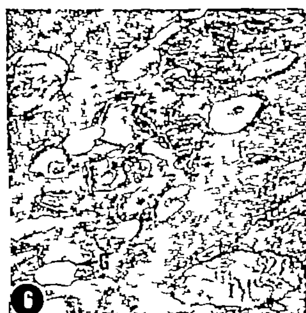


Fig. 6 A portion of an Intercalated disc of th myocardium f af er 490 hours of immu ; The on specialized region (G) of the interc lated disc is greatly dila ed. (X 27 000)



Fig. 7. An intercalated disc from the myocardium of a rat after a total of 1,550 hours of swimming. The intercellular space (arrow) in the myofibrillar insertion region is significantly widened. (× 54,000.)

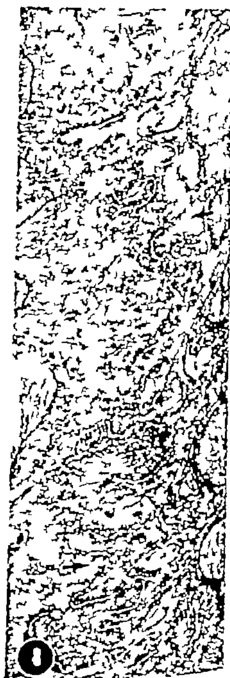


Fig. 8. Intercalated disc of the myocardium of rat after 1,550 hours of swimming. Cytoplasm adjacent to the intercalated disc appears electron-lucent (arrow). It appears that the myofibrils have pulled away from the surface of the intercalated disc. (× 31,000.)



Fig. 9. Intercalated disc from the heart of monkey 31 days after Coxsackie virus B infection. The intercellular space (arrow) in the myofibrillar insertion region is abnormally wide. (× 48,000.)



Fig. 10. Intercalated disc from the heart of mouse after three months of ethanol drinking. Note the widening of the intercellular space (arrow). (× 36,000.)



Fig 11 Intercalated disc from the atrial septum of an 8-year-old boy with congenital atrial septal defect. Note the dilation of the nonspecialized region (arrows) of the intercalated disc (× 33 000).

8) This translucency may be due to the fact that the filaments in the I band sarcomeres, at the end of the myocyte which normally are attached to the fibrillar sarcoplasm subjacent to the intercalated disc, had torn away from the surface of the intercalated disc. It is tempting to speculate that the widening of the intercellular space and the tearing of the I-band fibers could be due to mechanical tension associated with contraction of chronic [illegible]. In monkeys chronically infected with Coxsackie virus B_1 separation of the myofibrillar insertion region was also observed (Fig 9) The maximal width of intercellular space was about 75 mμ as compared to 25 mμ in the control monkeys. Widening of the nonspecialized regions of the intercalated disc was also noted in suckling mice after acute Coxsackie virus B_1 infection. Similar changes were also observed in the intercalated disc of mice after prolonged periods of ethanol ingestion (Fig 10).[8] The intercellular space in the myofibrillar insertion region was as wide as 1.0 μ in some areas. In atrial septal tissue obtained at surgery from a patient with a congenital atrial septal defect dilation of the intercellular space in the nonspecialized region of the intercalated disc was also seen (Fig 11) Of the tissues of 12 human hearts obtained at surgery and studied with an electron microscope only the tissue of this patient had an abnormal intercalated disc

The widened portions of the intercalated disc have been reported in isolated hearts perfused with hypertonic, low calcium, or EDTA[14] solutions. Widening of the intercellular space as observed in our experimental tissue does not seem to be the result of preparatory procedures since the control tissue similarly and simultaneously prepared did not display such changes. The pathogenesis of intercellular dissociation is unknown. The dissociation could be the direct effect of the metabolic changes under pathologic conditions or could be secondary to the pathologic changes in the myocyte. Under any of these circumstances, widening of the intercalated disc could be of significance especially when the electrophysiologic consequences are considered and better understood Whether or not the contractibility of the myofiber or the conduction of the excitation impulse is in any way affected by the structural alteration of the intercalated disc is a matter which requires investigation The conventional electrocardiographic recorders are too insensitive to detect such alterations in the wave spread of the electric activation process.

Summary

Myocardial tissue is divided into discreet cellular units by the intercalated disc at the intercellular boundary. The intercalated disc is structurally differentiated into four regions. The tight junction or nexal region of the intercalated disc has been considered the region of low electrical resistance, thus acting as a pathway for the electrotonic coupling between myocytes. Under various pathologic and physiologic conditions, there is a variable degree of separation of the intercalated disc. The role of the intercalated disc in the propagation of the excitation impulse in normal and diseased states is discussed.

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Atrial flutter sounds: Report of a case

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Reports of audible atrial sounds and their graphic recording in atrial flutter are rare. Since the first recording provided by Bennet and Kerr[1] in 1931 only 16 well-documented cases have been found in literature.[2] An additional case in which atrial sounds were clearly heard and recorded is reported here.

Case report

A 56-year-old housewife was admitted to the hospital on October 6, 1966, because of dyspnea and palpitations. She had been told of heart murmur ten years before and experienced dyspnea from exertion four years before admission.

Pertinent physical findings were regular pulse rate (120 beats per minute) blood pressure was 125/90. The lungs were clear. The first heart sound was accentuated at the pex. The second sound as loud at the lower left sternal margin. All along the left sternal edge an added systolic clicking sound as easily heard. A Grade 3/6 diastolic apical murmur and loud opening snap were also present. The liver was one fingerbreadth from the costal margin and there was no peripheral edema.

An electrocardiogram revealed trial flutter with an atrial rate of 230 per minute and 2 1 A V block.

Roentgenologic examination of the chest disclosed moderate enlargement of the cardiac shadow with an indentation of the left atrium on the barium-filled esophagus. There as also moderate bulging of the pulmonary conus and an increased hilar vascularity.

A phonocardiographic record as performed with Galileo Polyanalyzer PAB. Selective filtration of sounds in four frequency bands by band-pass filters re used. A loud first heart sound, an opening snap, and mid-diastolic presystolic pical murmur were recorded. I addition, sounds of moderate amplitude were present in all frequency bands t the rat of 230 per minute, at the pex, t the fourth left intercostal space t the sternal margin, and in the aortic and pulmonary area (Fig. 1). High frequency components of these sounds were best recorded in the pulmonary area, while low frequency components were most evident at the apex and the aortic area. Their greatest amplitude was in systole.

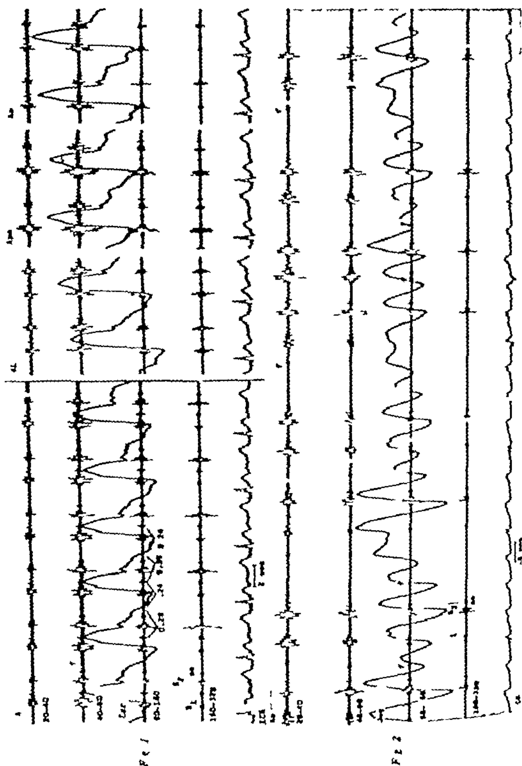
The following day higher degree A-V block spontaneously developed. Atrial sounds were no longer audible, but are still evident in the phonocardiogram (Fig. 2).

Discussion

Atrial flutter sounds have been described either as clicking[2,3,4] or soft, low pitched. The reported phonocardiographic features are widely different owing to the different recording technique and analysis of the frequency composition of such sounds is extremely difficult. Low frequency sounds are usually attributed to ventricular filling and vibration of ventricular musculature under the inrush of blood ejected from atrial systole (flutter gallop[5]). Movements of the A-V valves[3,4] or stretching of pleuropericardial adhesions, induced by atrial contraction have been postulated as the basis for clicking atrial flutter sounds.

In our case atrial flutter sounds were heard as high pitched and phonocardiographic analysis by pass-band filters showed both low and high frequency components.

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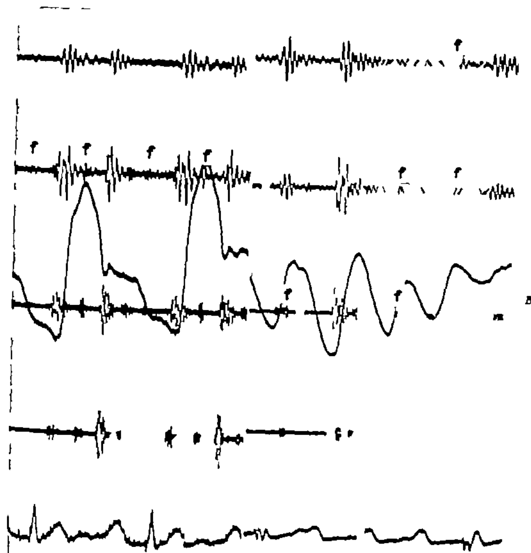


Fig. 3. A. Detail of Fig. 1. B. Detail of Fig. 2. Note the different phonocardiographic features of the two diastolic atrial flutter sounds in the second tracing of B.

The low frequency sounds were recorded in systole (Fig. 1) and at the end of longer diastolic periods (Fig. 2) while the medium-high frequency sound were most evident in systole and in protodiastole (Figs. 1 through 3). It seems reasonable to admit that different structures of the heart conceived as a cardiohemic system [12] are able to vibrate under each atrial contraction in the different phase of the cardiac cycle. In systole the atrium contracts against the closed mitral valve thus generating high frequency atrial sounds nevertheless, also during this period the blood in the ventricular cavities and in the great vessels is put into oscillation and this results in the production of low frequency components.[13] The latter are recorded well both at the base and at the apex of the heart (Fig. 1). At the end of longer diastolic periods the oscillations of the filled ventricle and the great vessels predominate and therefore only low frequency atrial sounds are generated (Figs. 2 and 3).

The systolic flutter sound was found to be of greater amplitude than the proto-

diastolic moreover it was observed that the interval of time between the two sounds was longer than the interval between the protodiastolic and the following systolic sounds (Fig 1) A reasonable explanation would be the different position and tension of the mitral valve leaflets in systole and in diastole

It has been repeatedly stated that only a high A V conduction ratio allows recognition of atrial flutter sounds owing to the *ensuing long diastolic silences.*[1,4] Although this is true when atrial sounds are low pitched (Fig 2) if they are high pitched they may be easily heard and recorded in the presence of low-degree A V block (Fig 1)

Summary

A case with mitral stenosis and atrial flutter in which atrial sounds were heard and recorded is reported The mechanisms generating such sounds are discussed

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Idiopathic right atrial enlargement in childhood

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Marked right atrial enlargement in childhood may occur in association with a number of cardiac anomalies. Congenital defects account for most examples; rheumatic tricuspid valve disease, acquired pulmonary hypertension, and primary right atrial neoplasms are rarer causes. The purpose of this paper is to report a child with a massive right atrial enlargement in the absence of any other cardiovascular abnormality.

Case report

B. K., a 6½-year-old Caucasian male, was referred to The Hospital for Sick Children for evaluation of an abnormal cardiac silhouette discovered on a preadoption roentgenogram. The child's recent history disclosed no symptoms relating to the cardiovascular system. Details of his infancy and early childhood were not available.

Physical examination revealed a healthy looking child with a weight of 21 kilograms, a height of 116 centimeters, a pulse rate of 86 beats per minute, and a respiratory rate of 20 beats per minute. Blood pressure and peripheral pulses were normal. There was no cyanosis and no evidence of congestive heart failure. The jugular venous pulse and pressure was normal. No thrills were present and there was no abnormal precordial pulsation. The first heart sound was normal. A Grade 2/6 vibratory ejection systolic murmur was detected at the left upper sternal border without any significant radiation. The second heart sound varied normally on respiration. The murmur was unaffected by postural changes and no other murmurs were produced. The lungs and other systems were clinically normal.

Laboratory investigations included a hemoglobin of 1 8 Gm. per 100 ml., a normal erythrocyte sedimentation rate and normal serum protein electrophoresis.

The electrocardiogram (ECG) (Fig. 1) revealed normal sinus rhythm and a frontal QRS axis of +75. The P waves were normal. There were low voltage QRS complexes over the right precordium. The tracing was considered to be normal for the child's age.

The chest roentgenogram (Fig. 2) showed moderate cardiac enlargement with a cardiothoracic ratio of 64 per cent and a prominent bulge to the right. On fluoroscopy the prominence at the right border could not be separated from the cardiac outline. Pulsation in this region was weak but synchronous with atrial contractions. At fluoroscopy it was impossible to determine whether the right atrium was enlarged or merely displaced by another enlarged cardiac chamber.

Cardiac catheterization excluded a left to right shunt by oximetry, and right heart pressures were all normal. The components of the right atrial pressure wave were reduced in amplitude, probably due to the large size of the chamber, but the mean pressure was normal. Simultaneous intracardiac right ventricular and right atrial ECG and pressures were obtained by means of an electrode catheter withdrawn from the right ventricle to the right atrium to exclude a minor degree of Ebstein's anomaly. A normal transition was obtained (Fig. 3).

The cineangiocardiogram showed marked right atrial and atrial appendage enlargement (Fig. 4). The tricuspid valve was in its normal relationship to the right atrium and right ventricle but both the valve and ventricle were displaced to the left by the dilated right atrium. No intra-atrial space occupying lesion was apparent. The right ventricle cavity was normal (Fig. 5). The left heart was normal with no evidence of atrial or ventricular septal defect.

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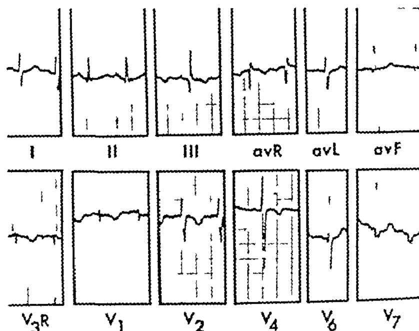


Fig. 1. ECG showing sinus rhythm. There is no evidence of hypertrophy of either atrium or ventricle.

Discussion

The diagnosis of idiopathic dilatation of the right atrium in this patient was established by exclusion of all the known causes of right atrial enlargement. There was no clinical, hemodynamic, or angiocardiographic evidence of atrial septal defect, partial or total anomalous pulmonary venous return, Ebstein's anomaly or other tricuspid valve disease, hypoplastic right ventricle, pulmonary stenosis or pulmonary hypertension. There was no evidence of mediastinal, pleuropericardial or pulmonary disease which might be responsible for local injury of the right atrial wall leading to dilatation. An intra-atrial tumor was excluded by selective angiocardiography.

Idiopathic right atrial enlargement has been described in adults. In 1955 Bailey[2] reported a 29-year-old woman with cardiomegaly, mild effort dyspnea, and paroxysmal arrhythmia. At thoracotomy, enormous dilation of the anterolateral portion of the right atrium was discovered while the remainder of the heart was normal. The atrial appendage was oversewn and a large elliptic segment of the right atrial wall was excised. This resulted in complete relief of the patient's symptoms. Bailey suggested that this condition was due to a congenital abnormality of the right atrial wall.

Pastor and Forte[3] described three asymptomatic adults with idiopathic enlargement of the right atrium. This was followed by the report of a middle-aged woman presenting with cardiomegaly and symptoms suggesting paroxysmal arrhythmia.[4] A period of atrial fibrillation followed an exploratory thoracotomy. In a subsequent operation a large portion of right atrial wall was excised with complete relief of her symptoms. The ECG which showed prominent P waves preoperatively returned to normal and atrial fibrillation did not recur. Sumner and his associates[5] described a further four asymptomatic adult patients with this condition. More recently Morrow and Behrendt[6] published the details of a surgical resection of a congenital aneurysm of the right atrial appendage in a 23-year-old housewife who had presented with cardiac enlargement and had repeated attacks of supraventricular tachycardia. Her symptoms were relieved by operation.

As in our patient, the initial presentation in all the previously reported cases followed the discovery of an abnormal cardiac



Fig. 2 Chest x-ray showing abnormal silhouette, with enlargement of the heart to the right The lung fields are normal.

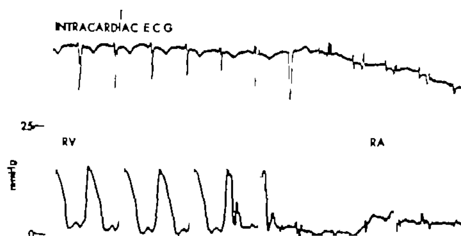


Fig. 3 Intracardiac ECG demonstrating the change from ventricular to atrial cavity complex, coinciding with the change in pressure on withdrawing from the right ventricle to the right atrium.

silhouette in a chest roentgenogram While the majority of patients with this condition are asymptomatic, they may present with symptoms suggestive of periods of arrhythmia. There are no diagnostic clinical findings in these patients, the ECG is essentially normal, although evidence of right atrial hypertrophy may be present The diagnosis can only be established by exclusion of all possible causes of right atrial enlargement. Investigation should include cardiac catheterization and angiocardiography It is essential that minor forms of Ebstein's anomaly be excluded by

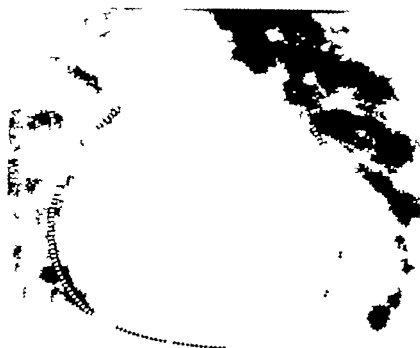


Fig 4 Angiocardiogram. The dotted line encloses the greatly enlarged right atrium.



Fig 5 Angiocardiogram. The dotted line encloses the right ventricular cavity shown i diastole.

the use of intracardiac electrocardiography.

Knowledge of the morphology of this anomaly is limited to gross descriptions of the right atrial anatomy in patients submitted to surgery and to microscopic studies on surgical specimens. In the case reported by Bailey the right atrium was symmetrically enlarged and was composed of an apparently normal atrial wall. One of Pastor and Forte's cases and the patient described by Saiguss and associates[4] showed diffuse dilatation of the right atrium. Microscopy in the former case revealed hypertrophy of the myocardial fibers and in the latter there was irregular hypertrophy and distribution of cardiac muscle fibers with abundant sarcoplasm and bizarre nuclei. Slight lymphocytic infiltration was present in some areas. Morrow and Behrendt distinguish between their patient, which they believe was an example of true aneurysm of the right atrium appendage and previous reports of idiopathic dilatation of the right atrium. The enlargement appeared to consist of a thin walled aneurysmal sac incorporating the whole appendage and containing an organized thrombus. The histologic examination of the aneurysm wall revealed that it was composed of fibrous tissue and attenuated myocardial fibers with an endothelial lining.

It is suggested that idiopathic dilatation of the right atrium is an isolated congenital cardiac anomaly. The uniformity of the clinical and laboratory features in the patients previously reported and in the present case is striking. This patient represents an example of this clinical entity presenting in childhood and might further suggest its congenital origin. In agreement with others, we also postulate that this condition is due to a congenital aberration which selectively involves the right atrial myocardium. The underlying etiology of this congenital malformation remains to be identified.

Information concerning the long term course and ultimate prognosis in this condition is based on rather short term observation in the cases reported in the literature. Of the 10 reported cases, seven patients had never experienced symptoms related to their heart lesion at the time of diagnosis, and while the majority were young adults, one patient had reached the age of 45. In contrast the remaining three patients had symptoms suggestive of periods of cardiac arrhythmia by their twenties. One of these patients developed such symptoms at the age of sixteen; seven years later when the diagnosis was made she was having frequent attacks of paroxysmal atrial tachycardia. Atrial flutter and fibrillation also occurred at this time. It is notable that in none of the reported cases were symptoms present during childhood.

A similar condition of idiopathic left atrial enlargement has been described in children with a high incidence of complicating atrial arrhythmias. In 1936 Semans and Taussig[7] reported isolated dilatation of the left atrium in a 5-year-old child with dextrocardia. The patient died of congestive heart failure probably precipitated by a supraventricular tachycardia. Pitts and Potts[8] subsequently reported successful excision of a left atrial diverticulum in a 2½ year-old boy with paroxysmal atrial tachycardia. More recently Parmley reported two children with left atriomegaly due to dilatation of the left atrial appendage. The course of the disease in one of these patients was complicated by multiple peripheral arterial emboli, metastatic cerebral vascular embolus, paroxysmal attacks of atrial tachycardia and atrial flutter with varying degrees of atrioventricular block. It is conceivable that a child with massive enlargement of the right atrium is potentially in danger of developing supraventricular arrhythmias and right atrial mural thrombus formation. The latter event may be further complicated by emboli to the pulmonary circulation or paradoxical emboli to the periphery in those patients with a patent foramen ovale.

Summary

The case of a 6½-year-old child with an isolated dilatation of the right atrium has been described. The patient was asymptomatic with normal auscultatory and electrocardiographic findings. An abnormal cardiac silhouette in a routine chest roentgenogram led to the diagnosis. Careful clinical and laboratory studies failed to

show an associated cardiac anomaly of congenital or acquired origin The angiocardiogram demonstrated a markedly dilated right atrium

Review of the literature suggests that idiopathic dilatation of the right atrium is *a rare but definite clinical entity A congenital origin of this condition has been* suggested While relatively benign the potential hazards of arrhythmia and intra atrial thrombosis with embolization exist

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Review

Cor triatriatum Pathologic anatomy and a consideration of morphogenesis based on 13 postmortem cases and a study of normal development of the pulmonary vein and atrial septum in 83 human embryos

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The classical form of cor triatriatum (triatrial heart) may be defined as a rare cardiac malformation in which the left atrium is subdivided into dorsal and ventral chambers by a fibromuscular diaphragm the dorsal chamber receiving the pulmonary veins, the ventral chamber giving rise to the left atrial appendage and leading to the mitral valve, and the communication between the dorsal and ventral chambers being large, small, or absent depending on the size of the opening(s) in the subdividing diaphragm.

However adequate the foregoing may be as a descriptive anatomic definition, it fails to elucidate more basic questions, such as What in fact, is the subdividing diaphragm? In more general terms, what is the morphogenesis of cor triatriatum?

These problems remain incompletely understood [1,2] and this paper is an attempt to clarify them

Material and methods

Thirteen postmortem cases of cor triatriatum obtained from three medical centers (Table I) were studied Cases 9 and 10 and Case 13 have been mentioned but not documented elsewhere The other ten cases have not been reported previously Only cases of classical cor triatriatum as defined in the introduction were included thereby excluding unrelated anomalies sometimes classified as types of cor triatriatum.

A study of the normal origin development, and incorporation of the pulmonary vein was done, based on 83 human embryos from the Minot Embryological Collection Harvard Medical School (Table II)

Results

Pathologic anatomy The principal findings in the 13 postmortem cases of cor triatriatum are summarized in Tables III

From the Congenital Heart Disease Research and Training Center Hektoen Institute for Medical Research, and the Department of Pediatrics, Northwestern University Medical School Chicago, Ill and the Division of Cardiology and Department of Pathology Children Hospital Medical Center and the Departments of Pediatrics, Pathology and Anatomy Harvard Medical School, Boston, Mass.

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Table I Postmortem cases of cor triatriatum

Case No.	Autopsy No.	Centers*	Sex	Age at death
1	260	CHDRTC	M	1 yr.
2	2 338	CHDRTC	M	20 10/11 yr.
3	720	CHDRTC	M	2 mo.
4	1 628	CHDRTC	M	9 mo.
5	1 124	CHDRTC	M	4 3/4 mo.
6	1 530	CHDRTC	M	8 mo.
7	1 109	CHDRTC	M	1 8/12 yr.
8	NK†	CHDRTC	NK	NK
9	56-82	CHMC	M	11 mo.
10	59 260	CHMC	M	4 mo.
11	65-244	CHMC	M	3 day
12	67 188	CHMC	M	1½ y
13	57 322	HSC	M	3 mo

*Centers CHDRTC, Congenital Heart Disease Research and Training Center, Chicago; CHMC, Children's Hospital Medical Center, Boston; HCS, Hospital for Sick Children, Toronto, Canada.
†NK, not known

Table II Human embryos studied from the Minot collection

Embryo No.	Length (mm.) or description*	Plane of section†	Thickness (µ)	Embryo No.	Length (mm.)	Plane	Thickness (µ)	Embryo No.	Length (mm.)	Plane	Thickness (µ)
2 157	Trilam. disc	O	8	2,036	11.0	T	8	2,037	20.0	S	[illegible]
1 586	Trilam. disc	T	10	2,161	11.1	T	10	744	21.0	T	[illegible]
2 146	1.2	O	10	189	11.5	T	15	2,304	21.7	T	[illegible]
40	2.4	F	8	2,303	11.5	T	10	631	22.0	S	[illegible]
2,313	2.6	T	8	2,273	11.7	T	10	871	22.8	T	[illegible]
317	Hor. 10	F	10	1 603	11.7	T	10	737	22.8	F	[illegible]
2 085	3.75	T	6	2 000	11.9	T	8	181	23.0	S	[illegible]
714	4.0	T	6	2,313	11.9	T	10	2 045	23.0	T	[illegible]
2,302	4.0	T	8	2,158	12.0	T	10	2 046	23.0	T	[illegible]
2,323	4.5	S	10	839	13.6	T	10	2 048	23.0	T	[illegible]
2,321	4.6	T	6	2,156	14.1	S	10	2,314	23.8	T	[illegible]
2 094	6.0	F	6	1,003	14.5	T	10	38	24.0	T	[illegible]
1,918	6.25	T	6	2 051	15.0	T	10	2 042	25.0	T	[illegible]
2,300	6.3	T	10	2,095	16.0	T	10	1 972	27.0	T	[illegible]
2,285	6.7	T	8	2,044	16.0	T	8	2,248	27.0	T	[illegible]
256	7.5	T	10	1 128	16.0	F	14	1 598	28.8	S	[illegible]
817	8.0	F	10	1,322	16.0	T	8	914	29.0	F	[illegible]
2 065	8.0	T	8	1 707	16.4	T	8	913	30.0	T	[illegible]
2,301	9.2	T	10	2,305	16.5	T	10	1 706	31.0	S	[illegible]
734	9.2	T	10	2 135	17.5	T	10	2,043	31.0	T	[illegible]
529	9.4	T	10	2,047	18.0	S	10	649	32.0	T	[illegible]
1 005	9.4	T	8	1 129	18.1	S	14	2,056	36.0	T	[illegible]
1 001	9.6	F	8	1 913	18.2	T	10	820	37.0	T	[illegible]
1 919	10.0	F	8	2,306	18.3	T	10	1 917	40.0	F	[illegible]
1 000	10.0	T	6	2,246	18.8	T	10	838	42.0	T	[illegible]
736	10.2	S	10	819	19.0	T	14	1,611	44.3	T	[illegible]
2,247	10.6	T	10	828	19.0	F	12	128	45.0	T	[illegible]
2,281	10.6	T	10	1,597	19.3	T	12				

*Trilam., trilaminar; Hor., horizon.[9-11]
†O, oblique; T, transverse (horizontal); F, frontal; S, sagittal.

Table III. *Salient pathologic findings in 13 cases of cor triatriatum*

Case No.	*Heart size*	*Right atrium*	*Atrial septum*	*Tricuspid valve*	*Right ventricle*	*Pulmonary valve*	*Openings in diaphragm*		*Mitral valve*	*Left ventricle*	*Aortic valve*
							No.	*mm.*			
1	E	H & E	Intact	E	H & E	E	1	3			S
2	E	H & E	ASD II	E	H & E	S	1	1	S		S
3	E	H & E	PFO	E	H & E	E	1	3	S		S
4	E	H & E	PFO	E	H & E	S	1	1	S		S
5	E	H & E	PFO	E	H & E	E	1	3	S	N	S
6	E	H & E	PFO	E	H & E	E	1	2	S	S	N
7	E	H & E	Intact	E	H & E	E	1	5	N	N	N
8	E	H & E	PFO	T At	S	S	1	3	E	E	E
9	E	H & E	Intact	E	H & E	E	2	1.0 & 0.5	N	N	N
10	E	H & E	PFO	E	H & E	E	2	2.0 & 1.0	N	N	N
11	E	H & E	PFO	E	H & E	E	0		Absent	Absent	A At
12	E	H & E	Intact	E	H & E	E	1	3	N	N	N
13	E	H & E	PFO	N	TW & SC	E		3 & 0.5	N	E	N

Abbreviations: *E*, enlarged; *H*, hypertrophied; *ASD II*, secundum type atrial septal defect; *PFO*, patent foramen ovale; *T At*, tricuspid atresia; *N*, normal-sized; *TW*, thick walled; *SC*, small-chambered; *S*, small (hypoplastic); *A At*, aortic atresia.

Table IV. *Associated abnormalities in 13 cases of cor triatriatum*

Case No.	*Associated abnormalities*
1	Partial anomalous pulmonary (pulm.) venous drainage: LUL pulm. vein to LSVC to left innominate (innom.) vein to RSVC to RA.
	Tetralogy of Fallot; PDA (5 mm. diameter); LSVC to Co S to RA; aberrant right subclavian artery; hypoplasia of RML of lung, with secondary dextrocardia; anomalous pulm. venous drainage from RML to IVC; anomalous pulm. artery from descending thoracic Ao to RML; displacement of LA appendage to right & posterior; intra-aortic band beneath ostium of right common carotid artery; brain abscess, large, left parietal, pseudomonas.
3	Bicuspid AV; deficient intercoronary commissure.
5	Coarc. of Ao, moderate, at ligamentum arteriosum; atresia of RA ostium of Co S; anomalous pulm. venous connection between Co S and LLL pulm. vein; VSD, high, very small (1 mm.).
7	PDA (3 mm.).
8	Tricuspid atresia, PFO, large (8 by 5 mm.); VSD, high, large (10 by 3 mm.); moderate Inf. & valvular PS with bicuspid PV; intra-aortic band from ostium of innom. artery to ostium of left subclavian artery.
9	Azygos lobe, right lung; two accessory spleenuli, each 3 mm. in diameter, in lienorenal ligament.
10	PDA (3 mm. diameter); malrotation of colon, cecum beneath gallbladder.
11	Atresia of ostium of common pulm. vein; extreme hypoplasia of LA; MV & LV absent; AoV atretic; PDA, left side, large (8 mm. circumference); aberrant right subclavian artery; persistent LSVC to Co S to RA; small accessory coronary artery from LPA; intersex male with abdominal testes, short blindly ending vagina & chromatin-positive buccal smear.
13	Complete d-transposition of great arteries; PDA, moderate (6 mm. circumference); high right coronary ostium (1 mm. above sinus of Valsalva); large valve of IVC.

Abbreviations in alphabetical order: *Ao*, aorta; *Coarc*, coarctation; *Co S*, coronary sinus; *Inf*, infundibular; *IVC*, inferior vena cava; *LA*, left atrium; *LLL*, left lower lobe; *LPA*, left pulmonary artery; *LSVC*, left superior vena cava; *LUL*, left upper lobe; *PDA*, patent ductus arteriosus; *PS*, pulmonary stenosis; *RML*, right middle lobe; *RSVC*, right superior vena cava; *VSD*, ventricular septal defect. Other abbreviations as in Table III.



Fig 1 A B Typical example of cor triatriatum (Case 7). A Exterior frontal view B Opened right atrium and right ventricle Ao aorta LV left ventricle PA pulmonary artery RA right atrium RV right ventricle SVC superior vena cava



Fig 1C Typical example of cor triatriatum (Case 7). The opened left heart chambers are described in the text LA left atrium LV left ventricle CPVC common pulmonary vein chamber

and IV and a typical case is presented in Fig 1 Viewed from the front the external appearance is highly characteristic (Fig 1,A and Table III) a left-sided heart (in 12 of 13 cases) normally interrelated chambers with no atrial or ventricular inversion (all cases) cardiomegaly (all cases) apex formed by the right ventricle indicating marked right ventricular hypertrophy and enlargement (Fig 1,B) (in 11 of 13 cases) left ventricle usually normal in size (in 5 cases) or mildly hypoplastic (in 5 cases) marked right atrial hypertrophy and enlargement (all cases) normally related great arteries (in 11 of 13 cases) dilatation of the pulmonary artery (in 10 of 13 cases) and the aorta normal in size (in 6 cases) or mildly hypoplastic (in 5 cases)

The right atrial septal surface usually appeared abnormal In this case (Fig 1 B) it is almost completely smooth there is no limbic ledge and virtually no demarcation between septum primum and septum secundum When obliquely probe patent (in 8 of 13 cases) the foramen ovale usually was distinctly smaller than normal This appeared to be related to the upward protrusion of the dorsal left atrial chamber By bulging upward, this chamber encroached on the foramen ovale from below and behind tending to narrow and close it as will be seen (Figs. 1 and III

The opened left heart chambers (Fig 1 C and D) show the dilated and hypertrophied common pulmonary vein chamber dorsal and obliquely *inferior* to the ventral chamber the subdividing fibromuscular diaphragm the opening in the diaphragm usually single (in 9 of 13 cases) and small (0.5 to 5 0 mm in diameter) located

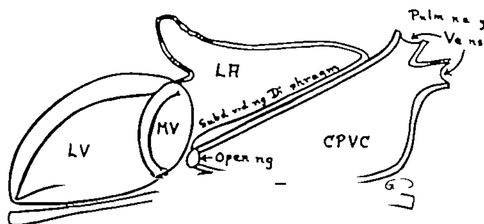


Fig. 1D Typical example of cor triatriatum (Case 7). Diagram of left heart chambers nd subdi iding d phragm. CPVC, common pulmonary ein hamber; LA left atri m LV left entricle MV mit l l

short distance behind the posteromedial commissure of the normal-appearing mitral valve and the normal-sized left ventricle.

The common pulmonary vein chamber usually is described as lying *above* the ventral chamber. This is a significant in accuracy. Dorsally the pulmonary veins may well protrude somewhat above the level of the ventral chamber. But as one proceeds ventrally the pulmonary vein chamber lies obliquely *below* the ventral left atrial chamber (Fig 1 C and D). It will be seen that this represents persistence of the normal embryonic relationship between these structures pulmonary vein below and left atrium above.

The anomaly. Viewed posteriorly and from the left (Fig. 2) the dorsal chamber strongly resembles the common pulmonary vein which has failed to incorporate normally into the left atrium. Viewed anteriorly and from the left (Fig 3,A) the fibrous continuity between septum primum and the subdividing diaphragm is striking.

It is illuminating to note that the continuity between septum primum and the diaphragm in cor triatriatum (Fig 3,A) appears essentially identical to the continuity between septum primum and the dorsal wall of the primitive left atrium in total anomalous pulmonary venous drainage (Fig. 3,B).

The foregoing findings strongly suggest that the subdividing diaphragm in cor triatriatum is composed of the wall of the common pulmonary vein dorsally (Figs 1C and 2) and the wall of the primitive left atrium ventrally (Fig 3).

Serial sections of the subdividing diaphragm in cor triatriatum (Figs 4A 4B and 4C) support this interpretation. Superiorly and ventrally the composition of the diaphragm is that of the left atrial free wall a thick layer of left atrial endocardium adjacent to the left atrial cavity external to this a prominent but discontinuous layer of striated left atrial myocardium and external to this a layer of fibrous tissue corresponding in part to the left atrial epicardium. Inferiorly and dorsally adjacent to the common pulmonary vein chamber the structure of the subdividing diaphragm is that of the common pulmonary vein this being most obvious in frontal sections (Fig 11 C). Beneath the focally thickened endothelium of this vein there is considerable smooth (nonstriated) muscle, which occasionally forms a discrete layer (Fig 4C). This smooth muscle is interpreted as the hypertrophied media of the common pulmonary vein. The bilaminar muscular structure of the diaphragm (striated and smooth) strongly supports the concept that it is composed of at least two structures, the left atrial free wall and the wall of the common pulmonary vein. Hence, the layer of fibrous tissue separating these muscular laminae is considered to have at least two origins the left atrial epicardium mentioned above

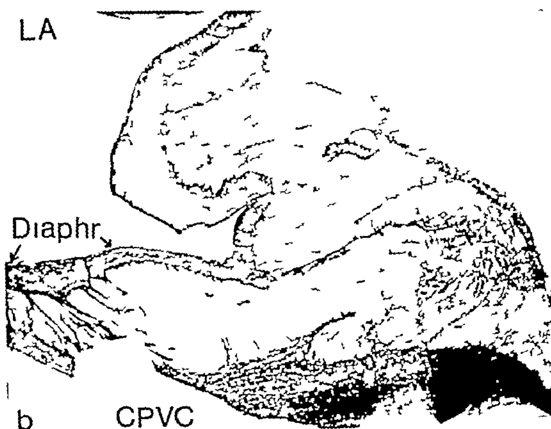


Fig 4B Histology of the diaphragm Low-power view (× 12) of the same case at junction of diaphragm left atrium (LA) free wall CPVC common pulmonary vein chamber

(Fig 5) this being the fourth reported case of cor triatriatum with tetralogy[7,8] and complete *d* transposition of the great arteries in Case 13 (Fig 6) the first documented case of cor triatriatum with transposition mentioned briefly elsewhere

Embryology The youngest embryo in this series (Table II) in which the pulmonary vein was identified with certainty had a greatest length of 4 6 mm (Streeter's[11] horizon 13 estimated age[11] since ovulation of 27 days) The common pulmonary vein is a small midline endothelial outgrowth from the dorsal wall of the still undivided primitive atrium (Fig 7,*A* and *B*) which extends a short distance into the mesenchyme of the early lung buds.

By 9 4 mm (horizon 16 estimated ovulation age 33 days) (Fig 7 *C*) the enlarging common pulmonary vein leaves the most rightward inferior and posterior (dorsal) corner of the left atrium The pulmonary vein passes immediately to left of a prominent mass of sinus ven tissue (Fig 7 *C*) Remaining a mid structure the common pulmonary v lies below septum primum, which als a midline structure and which is shown Fig 7,*D* It is noteworthy that at stage (33 days) the common pulmonary vein does not lie beside and to the left septum primum. Incorporation of the c mon pulmonary vein into the left at has not yet begun (Fig 7 *C*)

However by 11 9 mm. (horizon estimated ovulation age 35 days), poration has commenced (Fig 7,*E* common pulmonary vein has bee sorbed into the enlarging left atrium to the bifurcation or in this case trifurcation of the vein.

By 17 6 mm. (horizon 19 estima ovulation age 38 days) it is seen (Fig that the still midline common pulmon vein now does lie beside and to the of septum primum Incorporation of



Fig 4C. Histology of the diaphragm. Higher power view (X 100) of diaphragm of same case between Figs 4A and 4B to show greater detail. Verhoeff Van Gieson stain (Histologic sections by Natalie Daniels.) *LA* left atrium *CPVC*, common pulmonary vein chamber

left and right branches of the common pulmonary vein also has begun

Further branch incorporation progresses slowly and was found to be somewhat incomplete even at 45 mm (estimated age 63 days) this being the oldest embryo studied (Fig 7,G and Table II)

Frontal plane sections were illuminating At the 10 mm stage (horizon 16 33 days) they reveal that, as the pulmonary vein leaves the right lower posterior corner of the left atrium the vein passes beneath a relatively large mass of sinus venosus tissue (Figs. 8A 8B and 8C) and over the left horn of sinus venosus (future coronary sinus) Running rightward inferiorly and dorsally the common pulmonary vein soon lies directly beneath the plane of septum primum It then continues dorsally in the midline (Fig 8,D)

The mass of sinus venosus tissue above the common pulmonary vein merits attention. It is a "platform" for and the apparent origin of two structures (1) *septum primum* which grows upward from the left side of this platform and (2) *the left venous valve* growing upward from the right side

Sagittal sections at this stage (Fig 9)

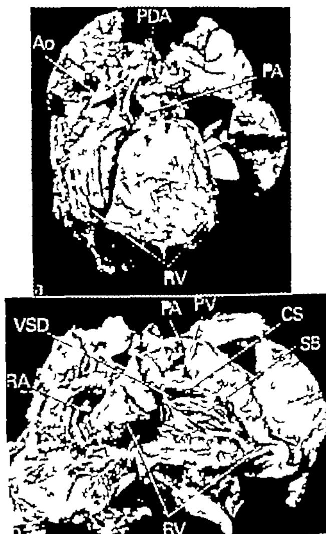


Fig 5 A B Tetralogy of Fallot with cor triatriatum and other associated anomalies (Case 2, Table II) A Exterior frontal view Since the pulmonary artery (PA) is of approximately normal size, this heart does not look like a tetralogy externally Patent ductus arteriosus (PDA) is seen. B Opened (RV) right ventricle and PA The pulmonary valve (PV) is tricuspid and only mildly smaller than normal. Considerable deviation of the crista supraventricularis (CS), typical of tetralogy is present. Hypertrophy of RV is massive. SB, septal band VSD ventricular septal defect

confirm that the common pulmonary vein leaves the left atrium through a narrow channel under and slightly behind the relatively large mass of sinus venosus tissue from which septum primum and the left venous valve develop

In subsequent development the platform of sinus venosus tissue disappears, leaving only its two outgrowths septum primum and the left venous valve (Fig 10) These sections (Figs 8 through 10) reveal that the true left sided leaflet of the valve of sinus venosus is bifid composed of the so-called septum primum to the left and the so-called left venous valve to the right (Fig 10) Also, the interseptovalvular space[11] is seen merely to be the cleft between these two components of the bifid true left venous valve (Fig 10,B). Our intention is to emphasize the developmental relationship between these structures, not to suggest changing their well entrenched conventional names (septum primum and left venous valve) which are used hereafter in the traditional sense but with the foregoing understanding in mind

Septum primum and the left venous

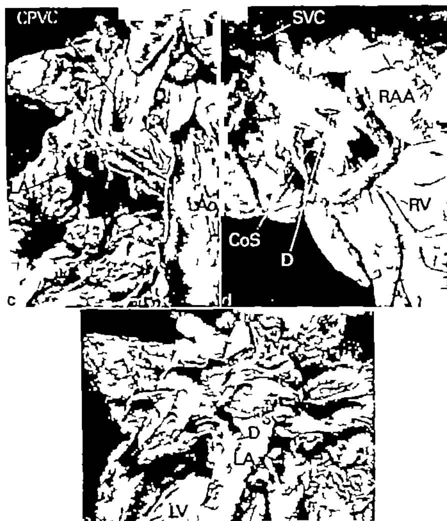


Fig. 5 *C D E*. Tetralogy of Fallot with cor triatriat m and other associated anomalies (Case 2, Table IV). *C*, Dorsal view of common pulmonary vei chamber (*CPVC*), with no visible outlet. *D* Opened right trium (*RA*) showing small defect (*D*), 1 mm. in diameter between *CPVC* and *RA* but not patent foramen ovale (see text). Enlarged coronary sinus (*CoS*) receives persistent left superior ena cava. Right atrial appendage (*RAA*) is grossly hypertrophied and enlarged. *E*, Opened left trium (*LA*) and left ventricle (*LV*) show second small defect (*D*), 1 mm. in diameter between *CPVC* nd *LA*

valve both are essentially extensions of the left wall of the inferior vena cava (Fig 10) Consequently both structures and the mass of sinus venosus tissue from which they arise (Fig 8) clearly represent the right horn of sinus venosus.

Thus, the common pulmonary vein normally grows out into the dorsal mesocardium through a narrow channel between right sinus horn (to the right and above the vein) and left sinus horn (to the left and below the vein) (Fig 8) e in a sling of sinus venosus tissue.

Discussion

Among the rarest of cardiac malformations, cor triatriatum comprises only approximately 0 1 per cent of congenital heart disease. Since the first clear-cut description of this anomaly by Church in 1868 only 86 definite cases have been reported over the intervening century to our knowledge (Table V) [78] A number of cases customarily cited as examples of cor triatriatum have been intentionally excluded usually because diagnostic re assessment very strongly suggested that

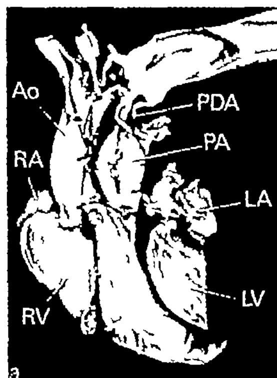


Fig. 6A Complete d-transposition with cor triatriatum (Case 13). Exterior frontal view. Right ventricle (RV) is not enlarged, despite presence of cor triatriatum, because transposition coexists. Left ventricle (LV) is disproportionately enlarged because of cor triatriatum, transposition, and patent ductus arteriosus (PDA). PA pulmonary artery; LA left atrium; RA right atrium; A aorta.

total anomalous pulmonary venous drainage to the right atrium was present, not classical cor triatriatum (Table VI). Our 10 unreported patients bring the total of definite cases to 96, there being a moderate male predominance (Table V): 46 male patients, 30 female patients, sex not stated in 20 cases (proportion of male to female 1.5 to 1.0).

Normal development. There have been a number of studies[11-19] of pulmonary venous development, some of which have included data concerning concomitant atrial septation. For brevity, detailed comparison of the findings of the present study with those of previous ones will be forgone. But attention must be focused on what appears to us to be the more important deficiencies of the usual accounts as, for example, are to be found in most embryology textbooks. These deficiencies proved highly relevant to cor triatriatum. Indeed, the pathologic anatomy of this anomaly seemed incomprehensible until certain aspects of normal embryology had been clarified (Figs. 1 to 10). (1) The common pulmonary vein does not originate to the left of septum primum and at the same level, as one usually is led to believe, but below septum

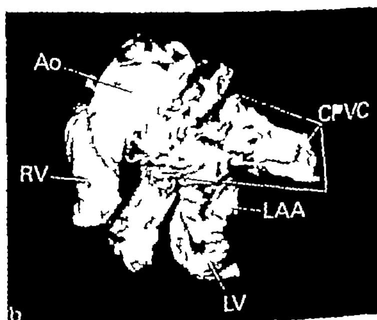


Fig. 6B Complete d-transposition with cor triatriatum (Case 13). Dorsal view of common pulmonary venous chamber (CPVC) and enlarged left atrial appendage (LAA). Note high right coronary ostium. RV right ventricle; LV left ventricle.



Fig. 6C. Complete d-transposition with cor triatriatum (Case 13). Opened left atrium (LA) and left ventricle (LV) showing two defects (Ds), 3 and 0.5 mm. in diameter and continuity between septum primum and diaphragm. CPVC, common pulmonary vein chamber.

primum and in the midline both the vein and the septum are essentially midline structures early in their development (27 to 33 days). (2) The mass of right horn sinus venosus tissue, from which both septum primum and the left venous valve develop and below which the common pulmonary vein runs early in its development, should be described. (3) The bifid structure of the true left venous valve apparatus (septum primum and the so-called left venous valve) and the nature of the space between these two components (the interseptovalvular space) merit clarification.

Morphogenetic hypotheses. There have been two principal hypotheses concerning the morphogenesis of cor triatriatum: (1) abnormal growth of septum primum,[17,22,23] i.e., *malseptation*, and (2) failure of incorporation of the common pulmonary vein into the left atrium,[18,21-23] i.e., *malincorporation*.

First expressed by Fowler[17] in 1881, the malseptation hypothesis is suggested by the continuity between septum primum and the subdividing diaphragm (Figs. 3,A and 6 C). Indeed, septum primum is an integral part of this diaphragm (Fig. 11). In 1905 Borst[22] (who coined the term cor triatriatum) suggested that the pulmonary vein develops to the right of septum primum in this anomaly instead of to the left, which he thought was normal. Plausibility was lent to this view by the observation that the common pulmonary vein chamber may lie predominantly to the right of septum primum (Figs. 3,A and 6 C). But the pulmonary vein chamber may also lie largely to the left of septum primum in cor triatriatum (Figs. 1 C and 2). Despite the differences between Fowler's[17] and Borst's[22] hypotheses, in both the subdividing diaphragm was regarded as septum primum.

But in 1949 Loeffler[23] emphatically rejected such interpretations because he found that septum primum is related normally to septum secundum in cor triatriatum (Fig. 3,A). Hence he concluded that the subdividing diaphragm cannot be an abnormally located septum primum. Since then most investigators have accepted the malincorporation hypothesis first published by Griffith[18] in 1903. While accepting this hypothesis in principle, Loeffler[23] appreciated that a basic question remained unanswered, namely, why does the common pulmonary vein fail to incorporate into the left atrium? He concluded that malincorporation is caused in all probability by a disturbance of the normal growth of the posterior wall of the left atrium and that the subdividing diaphragm is the posterior wall of the primitive left atrium.

However, the malincorporation hypothesis has not won universal acceptance. As noted by Sawyer and associates[3] in 1957, it fails to explain those cases in which the foramen ovale (or fossa ovalis) has been reported to be located in the medial wall of the dorsal chamber. Were the malincorporation hypothesis correct, one would expect the foramen ovale to open into the primitive left atrium (the ventral chamber), not into the dilated common pulmonary vein (the dorsal chamber). Case (Fig. 5,D) exemplifies this problem: a small opening between the common pulmonary vein chamber and the right atrium in the

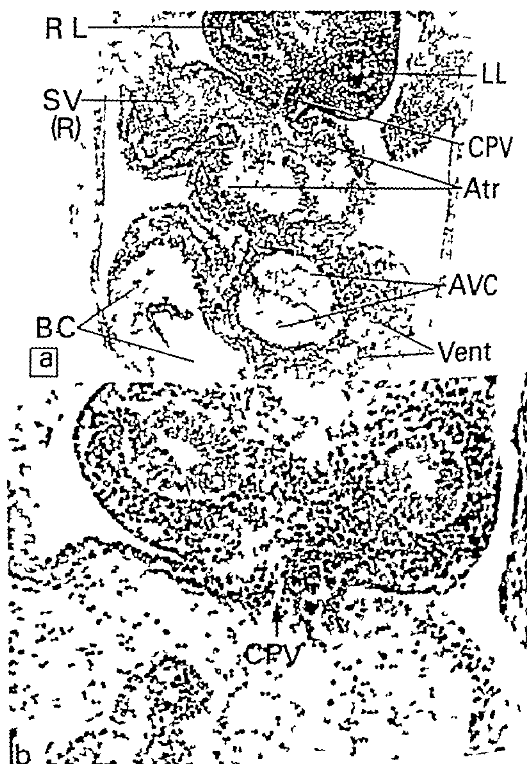


Fig. 7. *A*, *B*. Development of the pulmonary vein in man: horizontal plane (transverse) sections. *A*, Youngest embryo in which common pulmonary vein (*CPV*) definitely identified. (Embryo No. 2321, 4.4 mm; estimated ovulation age 27 days, section 257.) *Atr*, primitive undivided atrium; *AVC*, superior (ventral or anterior) and inferior (dorsal or posterior) endocardial cushions of the common atrioventricular canal; *BC*, bulbus cordis or future right ventricle; *LL*, left lung bud; *RL*, right lung bud; *SV(R)*, right horn of sinus venosus; *Vent*, ventricle of future left ventricle. (Alum cochineal and orange G stain; original magnification ×150.) *B*, Same embryo, close-up of *CPV*, common pulmonary vein. (Original magnification × 250.)



Fig. 7 *C, D* Development of the pulmonary vein in man, horizontal plane (transverse) sections. *C* Common pulmonary vein (*CPV*) leaves left atrium (*LA*) immediately to the left of a prominent mass of sinus venosus tissue (*SVT*) of right sinus horn. Incorporation of *CPV* into *LA* has not yet begun. (Embryo No. 1035, 9.4 mm., 33 days, section 331.) *E*, esophagus; *RVV*, right venous valve, i.e., right leaflet of valve of sinus venosus (*SV*); *LL*, left lung bud; *RL*, right lung bud; *LSVC*, left superior vena cava; *RA*, right atrium. (Borax carmine and Lyons blue stain; × 130.) *D* Same embryo (section 315). This section is 120μ above that shown in *C*. Note that *Sept I* is now well formed, that it lies above *CPV* and that both are essentially midline structures. *Sept I* and the left venous valve (*LVV*), the left leaflet of the valve of sinus venosus (*SV*), both have grown upward from the *SVT* shown in *C*. The space between *Sept I* and *LVV* is the so-called interrepto-valvular space. (Original magnification × 110.)

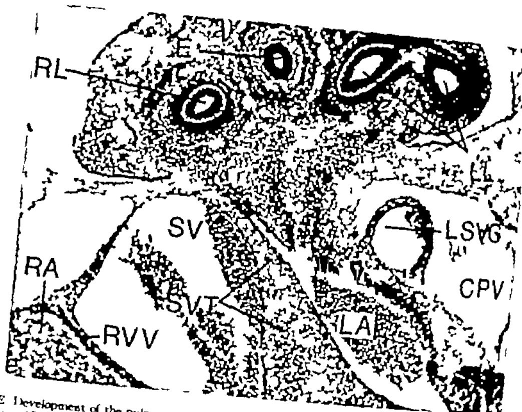


Fig 7E Development of the pulmonary er in man horizontal plane (tran verse) section. (Embr \ 28l 11 9 mm 35 days, section 510) Incorporation of the common pulmonary vein (*CPV*) is beginning *CPV* lies below *Sept I* immediately to the left of the prominent mass of sinus venosus tissue (*SVT*) from right horn of sinus venosus, f om which both *Sept I* and *LVV* (left venous valve) grow upward. *RA* right atrium *LA* left trium *LSVC* left superior ena ca *LL* left lung bud *RL*, right lung bud, *SV* sinus venosus, *RVV* right nou l *E*, esophagus. (Coch neal nd orange G tal original magnification X 1?0)

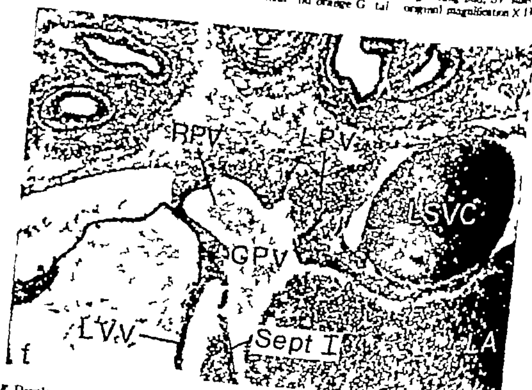


Fig 7F Development of the pulmonary vein man horizontal plane (tran verse) section. (Embr \ 28 17 6 mm., 38 days, section 789) Incorporation of common pulmonary vein (*CPV*) and its branches, right pulmonary vein (*RPV*) and left pulmonary vein (*LPV*), is progressing. *CPV* still midline, now does lie to the left of *Sept I* and its rightward ppendage, the so-called left venou v lve (*LVV*). The true left venous valve apparatus is bifid *Sept I* plus *LVV*. Left superior ena ca (*LSVC*) is st ll large. *LA* left atrium *E*, esophagus (Cochineal and orange G stain original mag ification X 130.)

general region of the fossa ovalis. The critical point, however, is that this is not the true foramen ovale. In this case as in all others, to our knowledge septum primum is continuous with and part of the diaphragm (Figs. 3,*A*, 6,*C*, and 11); hence the true foramen ovale, if patent, must open into the ventral chamber. In this case (Fig. 5,*D*) the dorsal chamber opens into the right atrium through an *abnormal* communication between the pulmonary vein chamber and the right sinus horn part of the right atrium. Communications between the pulmonary vein and various parts of the sinus venosus are well recognized (e.g., Case 5, Table IV).

Thus, we think that reports of the foramen ovale opening into the dorsal chamber are misinterpretations: abnormal communications, not the true foramen ovale.

The foregoing realization appeared to make the malincorporation hypothesis acceptable, but the reasons for malincorporation remained obscure. Specifically, why should a growth abnormality of the dorsal left atrial wall, as postulated by Loeffler,[19] result in a diaphragm invariably continuous with septum primum, i.e., why should a free wall abnormality always involve the septum? On the other hand, the malseptation hypothesis seemed untenable. If the subdividing diaphragm were septum primum, why would the pulmonary veins not drain freely into the right atrium, resulting in total anomalous pulmonary venous drainage instead of cor triatriatum?

This, then, was the riddle which emerged from the anatomic part of this study, indicating the necessity of an embryologic investigation (Table II).

Entrapment hypothesis. The anatomic plus the embryologic findings suggest that the common pulmonary vein fails to incorporate normally into the left atrium, resulting in cor triatriatum, because the

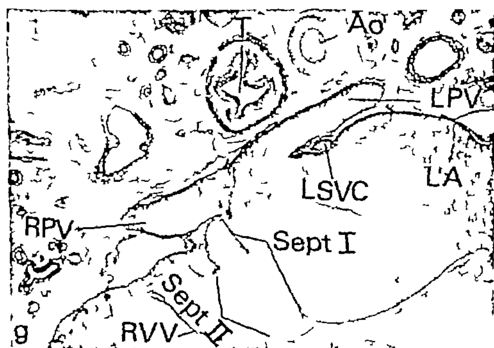


Fig. 7G. Development of the pulmonary vein in man, horizontal plane (transverse) section. (Oldest embryo in the series, N 2128, 45 mm., estimated age 63 days, section 2035.) Pulmonary vein still midline as always, and pulmonary vein branches still not fully incorporated into left atrium (*LA*). Left superior vena cava (*LSVC*) regressing. *Sept II* present, and large ostium secundum above *Sept I*. *RVV*, right venous valve; *RPV*, right pulmonary vein; *LPV*, left pulmonary vein; *T*, trachea. (Cochineal and orange G stain; original magnification ×40.)

Table V Previously reported cases of classical cor triatriatum

Year	Author(s)	Sex	Age at death
1868	Church	F	38 y
1881	Fowler	M	42 yr
1890	Preiss	F	11 yr
		M	3 y
1896	Griffith	NK	NK
1899	Martin	NK	NK
1903	Griffith	M	48 yr
1904	Potter & Ranson	M	NK
1905	Borst	F	38 yr
1907	Hosch	F	25 days
1911	William & Abrikossoff	M	11 yr
1933	Helwig	M	58 y
1934	Faber	M	2 yr
1940	McLester et al.	M	18 y
1941	Pfeffer	F	5 wk.
1949	Loeffler	F	70 y
1950	Parsons	M	NK
1951	Edwards et al.	F	6½ mo.
1952	Barnes & Finlay	M	16 mo.
1953	Doxiadis & Emery	F	10 wk
1954	Pedersen & Therkelsen	F	29 y
1954	Haarscher et al.	F	8 mo
1955	Hartmann	M	12 y
1955	Becu et al.	F	5 mo.
1955	Petit & Déchamps	M	14 mo.
1956	Lewis et al.	M	23 y
1956	Vineberg & Gualloreto	F	21 yr
1956	Nash & Mackinnon	M	7 wk.
1957	Barrett & Hickie	M	17 yr
1957	Cottier & Tobler	M	NK
1957	Vossenaar	NK	NK
1957	Sawyer et al	F	2 yr
1957	Maxwell et al.	M	7 wk.
1957	*Marincurr*	*M*	*21 mo.*
1957	Varcasia & Pentane	F	2 mo.
		F	4 y
1957	Chaptal et al.	NK	NK
1958	Latour et al.	F	2 yr
1958	Seavey & Dorney	M	3 yr
1959	Belcher & Somerville	F	28 yr
1960	Niwayama	M	2½ yr
		M	3 mo.
		F	9 wk.
1960	Edwards	NK	NK
1960	Gouslos & Cotton	F	2½ yr.
1960	Therkelsen & Fabricius	F	33 yr
1961	Redo & Goldberg	M	23 mo.
		NK	9 yr.
1961	Darke et al.	F	9 yr
1961	Abedrop et al.	M	9 yr
1961	Anderson & Varco	F	3 yr
1961	Varonier	F	11 da
1962	Magidson	F	6 yr
1962	Lam et al.	F	30 y
1962	Slade et al.	F	33 yr
1962	Grunebaum & Yahini	M	6 mo.
1963	Jegler et al.	M	4 mo.
		F	3 y
		M	16 mo.
1963	LaSalle et al.	M	17 mo.
1963	Nadas	M	11 mo
		M	4 mo
		NK	NK
	(2 cases)	M	5 yr.
1963	Sherman	M	3 mo.
		NK	NK
		M	18 mo.
1963	Lucas et al.	M	19 mo
1963	Papaioannou et al.	F	17 mo.
1964	Gordon et al.	F	12½ mo.
1964	Miller et al.	M	19 y
1965	McGuire et al.	M	5 yr.
1965	Hudson	NK	NK
1965	Guerin & Poisson	NK	NK
1966	Gasul et al.	NK	NK
		F	22 mo
1966	Somerville	M	51 yr
1967	Beller et al.	M	8½ mo
1967	Perry et al.	M	3 mo
1967	Keith et al.	NK	NK
	(6 cases)	NK	4 yr
1967	Nagao et al.		

NK, not known

Table VI Cases not regarded as classical cor triatriatum

Year	Author(s)	Probable diagnosis*
1829	Andral	Uncertain, but not cor triatriatum
1896	Rolleston	Supramitral band
1908	Stoeber	TAPVD to RA
1929	Patten & Taggart	TAPVD to RA via Co S
1930	Palmer	TAPVD to RA via Co S, plus sinus septal defect
1931	Hagmanner	TAPVD to RA via Co S
1956	Árvay & Szilas	TAPVD to RA via Co S plus sinus septal defects
1960	Niwayama	Cases 1 and 3 probably TAPVD to RA
1963	Sherman	Case 4 supramitral band

*TAPVD, total anomalous pulmonary venous drainage; RA, right atrium; Co S, coronary sinus.

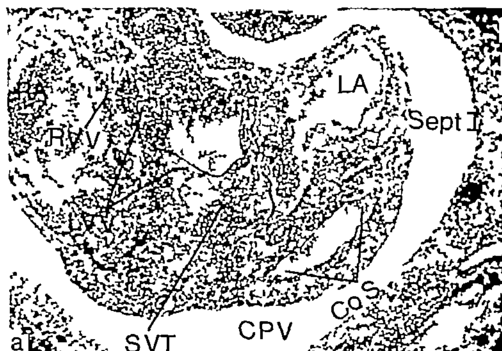


Fig. 8A. Frontal plane section. (Embryo No. 1919, 10 mm, 33 days, section 674.) Common pulmonary vein (*CPV*) grows out from left atrium (*LA*) in a medial, dorsal, and inferior direction. *CPV* passes under overhanging ledge of sinus venosus tissue (*SVT*) derived from the right sinus horn. Both *Sept I* and *LVV* grow upward from this platform of *SVT*. Note that the *CPV* lies directly beneath *Sept I*. The left horn of sinus venosus, future coronary sinus (*CoS*), is still large. *RVV*, right venous valve; *LVV*, left venous valve. (Cochineal and orange G stain, original magnification × 130.)

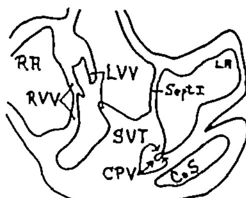


Fig. 8B. Tracing of Fig. 8A to make clear the superior-inferior relation between *Sept I* and *CPV*, both midline structures at this age. See Fig. 8A for abbreviations.

pulmonary vein becomes entrapped by the relatively large mass of right horn sinus venosus tissue beneath which the vein runs early in its development (Figs. 7 to 9). The left atrial ostium of the common pulmonary vein appears to get "roofed in" by fibroelastic tissue from the right sinus horn thereby preventing normal incorporation. This is where we think the prominent layer of fibroelastic tissue above the ostium of the common pulmonary vein comes from—well seen in serial sections of the subdividing diaphragm (Fig. 4,A).

Being endothelium, sinus venosus tissue has the well-recognized endothelial property of forming fibroelastic tissue throughout the heart. Examples of fibroelastic tissue derived from endothelium include the left and right venous valves, septum primum, the atrioventricular valves, pars membranacea septi, and the semilunar valves.

The embryologic data appear to clarify two of the most puzzling anatomic problems in cor triatriatum: (1) Why may the common pulmonary vein chamber lie predominantly to the left of septum primum (Figs. 1 C and 2) or largely to the right of this septum (Figs. 3, 4 and 6 C)? Since the embryonic location of the common pulmonary vein is beneath septum

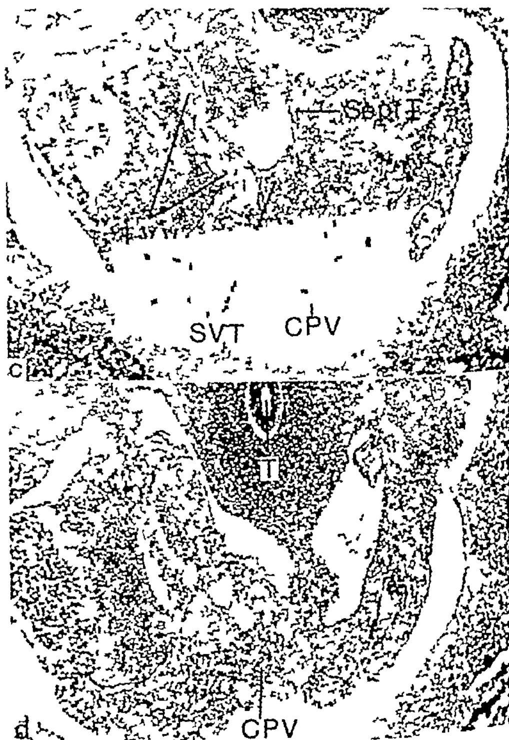


Fig 8 C, D Frontal plane sections. C (Same embryo, same stain, same magnification as Fig 8A) Section 6[illegible] 48μ dorsal to view seen in Fig 8A Small common pulmonary vein (*CPV*) is still directly beneath *Sept I* and the mass of sinus venosus tissue (*SVT*) from which both *Sept I* and the left venous valve (*LVV*) develop *D* (Same embryo same stain, same magnification as Fig 8A) Section 685 40μ dorsal to Fig 8B *CPV* is now in dorsal mesocardium, heading toward the lung buds the midline location of the *CPV* being indicated by reference to the trachea (*T*).

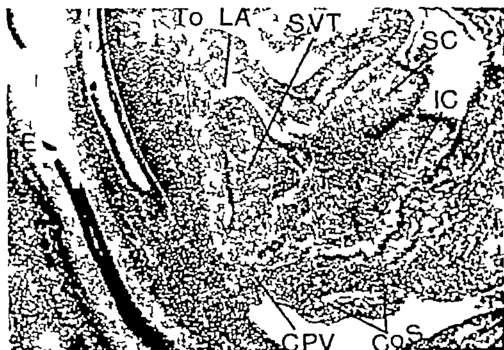


Fig. 9 Sagittal section. (Embry No. 736, 10.2 mm., 33 days, section 138.) Common pulmonary vein (*CPV*) leaves the left atrium (*LA*) by passing beneath and behind the aforementioned mass of sinus venosus tissue (*SVT*), and above the left sinus horn, i.e., future coronary sinus (*CoS*). At this age, *CPV* is very inferior in the same horizontal plane as the inferior cushion (*IC*) of the common atrioventricular canal. The midline location of *CPV* is confirmed by the trachea (*T*) and esophagus (*E*), both of which are sectioned longitudinally. Thus, *CPV* is midline structure inferior both to *LA* and *Sept I*, this being highly relevant to anatomy of cor triatriatum. *SC*, superior cushion. (Borax carmine and Lyons blue stain, original magnification × 130.)

primum (Fig. 8), the stenotic and dilating common pulmonary vein may protrude upward on either side of the overriding septum primum. (2) Why is septum primum continuous with, indeed part of, the subdividing diaphragm? As the stenotic and dilating common pulmonary vein bulges upward beneath septum primum, and as the platform of sinus venosus tissue beneath septum primum and the left venous valve becomes reduced in size (see Figs. 8 and 10), the common pulmonary vein must become intimately related with septum primum (Fig. 11). Dilatation of the pulmonary vein seen in Figs. 8,*A* through *C* would then result in the picture seen in Fig. 11.

The origin of the common pulmonary vein appears normal in cor triatriatum. The course of the common pulmonary vein in this anomaly likewise seems normal relative to septum primum and the left atrium, i.e., just as in the embryos. Hence, the common pulmonary vein seems normal per se in cor triatriatum.

The abnormal appearance of the right atrial septal surface in cor triatriatum (Figs. 1 *B* and 5,*D*), the location of the mass of right sinus horn tissue above the pulmonary vein in the embryo (Figs. 7 to 9), and the prominent fibroelastic layer above the stenotic or atretic common pulmonary vein in the pathologic heart specimens (Fig. 4,*A*) all suggest that the basic abnormality involves endothelium of the right horn of sinus venosus, not endothelium of the common pulmonary vein. But an experimental model, not presently available, is needed to explore this possibility further.

Available data strongly suggest that both of the conflicting morphogenetic hypotheses are in a sense correct although the "malseptation" concept appears to be the more basic of the two. Curiously, these two hypotheses have always been viewed

Fig 10 A B Septum primum, the left venous valve and the interseptovalvular space. (Embryo No. 911, [illegible] mm 56 days) *A* Frontal section 490 *B* Frontal section 491 20μ dorsal to *A* By this age, the [illegible] of sinus venosus tissue (Fig 8) has disappeared, leaving only its progeny: *Sept I* and *LVV* Both comprise the [illegible] left-sided leaflet apparatus of the valve of sinus venosus. Both are direct intracardiac extensions of the left [illegible] of the inferior vena cava (*IVC*) and the cleft between them is the intersepto-valvular space. Normally therefore *Sept I* the left venous valve (*LVV*), and the right venous valve (*RVV*) all appear to be derived from right sinus horn tissue. *SVC* superior vena cava *LA* left atrium *CoS*, coronary sinus *LPV* left pulmonary vein, *RPV* right pulmonary vein *PFO* patent foramen ovale. (Borax carmine and Lyons blue stain; original magnification × 100)

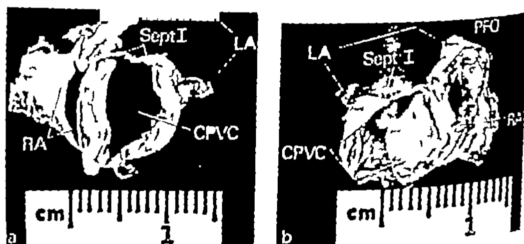


Fig 11 A B. Frontal section of Case 10 (Tables I III and IV). *A* Anterior view *B* Posterior view *RA*, right atrium *LA* left atrium *CPVC*, common pulmonary vein chamber *PFO* patent foramen ovale *Sept I*, septum primum.

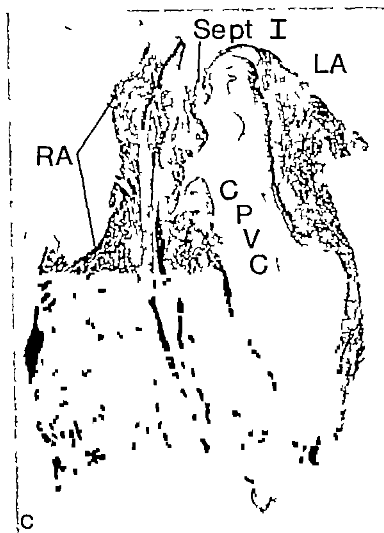


Fig. IIC. Photomacrograph of frontal section of Case 10 (Tables I, III and IV). This confirms that the left atrium (*LA*) is superior that the common pulmonary vein chamber (*CPVC*) is inferior and that *Sept I* forms part of the roof of the *CPVC*. (Verhoeff Van Gieson stain original magnification × 15.)

is mutually exclusive either/or alternatives. Tissue intimately related to septum primum is the apparent cause of malincorporation of the common pulmonary vein into the left atrium thereby producing cor triatriatum

Summary

The principal pathologic findings in 13 cases of classical cor triatriatum were presented including the first documented case of complete transposition of the great arteries and the fourth reported case of tetralogy of Fallot with cor triatriatum

Findings relevant to this anomaly were reported from a study of normal development of the pulmonary vein and atrial septum based on 83 human embryos. Attention was focused on the origin course and incorporation of the common pulmonary vein and on the origins and development of septum primum the left venous valve, and the intersepto-valvular space.

The pathologic and embryologic findings strongly suggest that cor triatriatum results from entrapment of the left atrial ostium of the common pulmonary vein

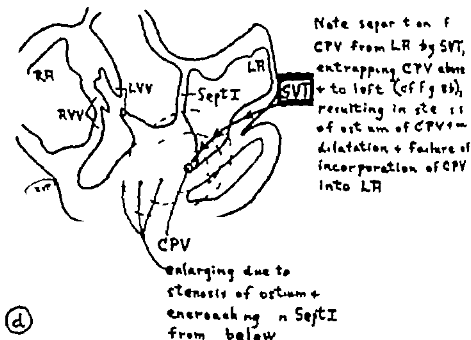


Fig 11D Diagr mmatic presentation of entrapment hypothesis If the common pulmonary ve (CPV) Fig 8 A C ere greatly dilated the ppearance would be essentially that of Fig 11 A-C. Entrapment of the left trial (LA) ostium of the CPV by the sinus venosus tissue above nd to the left ould prevent incorporation of the CPV t LA Stenosis of CPV ostium and dilatation of CPV would ensue. The location of the CPV bene th Sept I would expla n the participation of Sept I in the diaphragm, as in Fig 11 A-C. The proposed sinus venosu endothelium t form fibroelastic ti sue would explain the histology of the diaphragm, in particular the fibroelastic tissue above and t the left of the ostium of the CPV (Fig 4A). RA right atrium LVV left venous v RVV right venous valve

by tissue of the right horn of the sinus venosus from which septum primum develops, leading to failure of incorporation of the common pulmonary vein into the left atrium during the fifth embryonic week.

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The clinical course of patients with severe "rheumatic" mitral insufficiency

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Surgery for mitral insufficiency has now progressed to a point where operation leading to clinical improvement can be carried out with an acceptable operative risk. However, there are still very real problems concerned with various prosthetic valves and late complications of the operation. In view of the present stage of surgery for mitral valve insufficiency, it is important to know exactly what is the clinical course of patients with this condition under medical management, so that we can better select the place for surgery in our patients. It is surprising how little attention has been paid to this recently. Most of our concepts today are based on articles written several years ago when the criteria for the clinical diagnosis of mitral insufficiency were relatively crude. Many of the published reports are concerned with patients in whom a significant degree of mitral stenosis coexisted with insufficiency. There have been, on the other hand, many articles published dealing with surgery in this condition, the use of various prosthetic and other devices as valve replacements, as well as hemodynamic and angiographic studies. Articles dealing with the selection of patients for surgery are largely based on the conventional clinical wisdom of the past or on rather arbitrary and by no means infallible hemodynamic criteria, and are colored by the degree of enthusiasm or skepticism currently afflicting the authors. In particular, there is a paucity of reports dealing with what happens to patients with mitral incompetence under medical management who are already symptomatic in varying degrees when they come under observation. Many of the published follow-up studies deal with the course of rheumatic heart disease following acute rheumatic fever. Such studies, while valuable, poorly lend themselves to comparative studies of the course of the disease after surgical treatment, as has been shown in an analogous situation when attempts were made to compare the results of surgical therapy for mitral stenosis with medical management of the disease.

Our interest in this subject was stimulated by observing a number of remarkable patients, of whom the following is an example. A young man of 23 (A. M.) with severe rheumatic mitral insufficiency was referred for medical advice as to the advisability of his marrying. A murmur had been present since the age of 9 when he had

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Fig. 1. Posteroanterior and lateral roentgenograms of Patient A. M. show enormous enlargement of left atrium posteriorly and to the right, and apparent enlargement of left and right ventricles.

rheumatic fever. Since then his symptoms slowly increased so that at the time of our examination he had dyspnea on slight exertion and easy fatigue. His liver was palpable. His heart was enormous by roentgenogram (Fig. 1), chiefly in the region of the left atrium, and his electrocardiogram (ECG) showed combined ventricular enlargement (Fig. 2). Because satisfactory surgical treatment was not then available he was given a dubious prognosis and not much else. Ten years later this man was happily married with 2 children; he had less dyspnea and fatigue, and his liver was no longer palpable. Roentgenogram of his heart and ECG were unchanged. His improvement was largely due to the fortunate fact that he was enabled to budget his energy better, for he had been promoted from a bank teller to the sedentary life of a vice-president, keeping "banker's hours."

A year later he did deteriorate, and surgery now being available, he underwent mitral valve replacement of a grossly incompetent nonstenotic valve. He has had marked improvement, but little or no change in heart size since giant atria do not diminish in size without surgical excision.

The observation of this and similar patients raised the question as to how frequently do symptomatic patients follow such a benign course, and how often do they deteriorate progressively. This article therefore will reassess the clinical profile and course of adult patients with severe rheumatic mitral incompetence compared to those with mitral stenosis, and a small group of patients who had ruptured chordae or papillary muscles.

Material and methods

Group A includes 42 patients, personally seen and followed by one of us (L.B. Ellis) over a period of years, with the clinical diagnosis of pure or predominant mitral insufficiency. Classified in this group were patients who had an apical holosystolic murmur of Grade III or greater in intensity. An apical diastolic murmur might or might not be present; when present it was low-pitched and rather early, frequently following a third sound. An opening snap was absent. The etiology was assumed to be rheumatic and there was no clinical evidence of aortic or of any major complicating conditions. These patients were se-

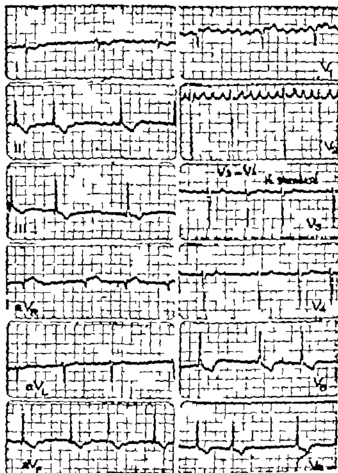


Fig 2 ECG of Patient A M showing atrial flutter-fibrillation, and left ventricular hypertrophy with a broad axis of plus 100 degrees (combined ventricular hypertrophy)

lected from a much larger group seen in medical consultation usually with a question of cardiac surgery in mind Most of these patients were seen first by the author prior to 1961 at a time when there was no definitely acceptable surgery for mitral insufficiency The diagnosis of uncomplicated severe mitral insufficiency was confirmed in 6 of these patients at subsequent cardiac surgery in 5 more by left heart catheterization and angiography and in 3 others by postmortem examination

Group B includes 115 consecutive patients who underwent cardiac surgery by D E. Harken They were found at surgery to have severe mitral insufficiency with trivial or no mitral stenosis. (The mitral valve area was estimated to be 4 cm² or greater in all but 6 patients in whom it was estimated to be from 2 5 to 3 9 cm² or the description of the surgeon was "very slight minimal or no stenosis") The etiology was assumed to be on a rheumatic basis, and there was no evidence of any other significant valvular or cardiac lesion. Twenty-eight of these were operated by closed mitral valvuloplasty and the remaining 87 underwent open cardiac surgery with cardiopulmonary bypass. The majority of these patients had not been observed for any extended period of time by the authors prior to their referral for cardiac surgery The purpose of selecting this group was to set up a standard of comparison between patients who have proven mitral insufficiency and the Group A patients in whom the diagnosis was based on clinical criteria.

Group C includes 138 consecutive patients who underwent closed mitral valvular

plasty and who were shown at surgery to have severe mitral stenosis without evidence of significant mitral insufficiency other valvular disease or cardiac disease of other nature. This group was selected for comparison with the two preceding groups.

Group D includes 13 patients who were found at open heart surgery to have ruptured chordae tendineae or papillary muscles.

The classification used in all the groups was that which has previously been described.[3] To avoid confusion with Groups A, B C, and D of this study what were called Groups 1 2 etc in the original study are designated as Class 1 2 etc. in this paper Class 1 is comprised of patients who are asymptomatic on ordinary activity Class 2 includes patients with moderate, but static, cardiac limitation of cardiac reserve, able to carry on sedentary activity Class 3 is comprised of patients whose symptoms are clearly progressive Class 4 is comprised of patients who are cardiac invalids, in heart failure or only kept out of failure by a rigorous medical regimen. This classification corresponds fairly closely to the New York Heart Association classification, but takes into account a dynamic view of the patient's clinical picture.

The description of the roentgenographic findings in Group A is based on cardiac fluoroscopy personally done by the senior author The roentgenographic findings in Groups B C and D are based on cardiac fluoroscopy by the hospital roentgenologist plus review of x-ray films (posteroanterior lateral, right, and left obliques) by the authors.

The ECG's were reviewed by the authors, using the criteria of Sokolow and Lyon.[3-4] Because many of the patients were under a strict cardiac regimen, including digitalis and diuretic drugs, S-T and T segment deviations were not employed as criteria for the diagnosis of ventricular enlargement. Left ventricular hypertrophy was diagnosed if one or more of the following criteria existed an R wave in V greater than 26 mm an R wave in V or V plus an S wave in V exceeding 35 mm. the sum of R and S exceeding 24 mm. or an R wave in aV greater than 11 mm.

Right ventricular hypertrophy was diagnosed on the basis of one or more of the following R/S in V greater than 1 an R wave in V greater than 7 mm. qR in V_1 or a persistent RS pattern across the precordium

Combined ventricular hypertrophy was diagnosed when criteria for both left and right enlargement were present or when left ventricular enlargement existed with a frontal axis of plus 90 degrees or greater

These criteria for ventricular enlargement were admittedly arbitrary and no claim that they are highly accurate is being made They were merely adopted to set uniform standards of comparison Vector cardiograms were not done with sufficient frequency to permit valid analysis.

This study will not include a discussion of the physical findings or the clinical diagnostic criteria of mitral insufficiency because Group A patients were obviously selected largely on the basis of predetermined criteria of physical findings, and in the other groups the nature of the study was such that many of the patients did not have detailed observations made by a single observer

Results

Groups A and B compared to C It is clear from a comparison of Groups A and B that the two groups were similar in every way (Table I)

There was a preponderance of female patients in Groups A and B but the difference was of borderline significance when compared to those with pure mitral stenosis (Group C) (Groups A and B compared to C $p = 0.05$ Group B compared to C $p = 0.25$) This is in contrast to findings reported by others,[2,3] although Jhaveri and associates[4] and Ross and associates[6] had more females than males in their series.

The average age of patients coming to surgery was the same for patients with mitral insufficiency and mitral stenosis as well as for those in Group A when first observed In this group however there was a tremendous range of ages regardless of the degree of cardiac disability when first seen

Both groups of patients with mitral insufficiency had a significantly higher incidence of a history of rheumatic fever than those with mitral stenosis ($p < 0.001$)

A history of subacute bacterial endo-

Table I Groups A, B, C, and D compared

Variables	Group A Private series		Group B "Rheumatic mitral insufficiency—surgical series		Group C Pure mitral stenosis—surgical series		Group D Ruptured chordae or papillary muscle	
	No.	%	No.	%	No.	%	No.	%
Total no. of patients	42		115		138		13	
Average age (years)*	43		44		44		57	
Sex								
Female	29	69	92	80	119	86	2	15
Male	13	31	23	20	19	14	11	85
Degree of disability								
Class 1	12	29	0		0		0	
Class 2	18	43	0		0		0	
Class 3	6	14	63	54	87	62	2	15
Class 4	6	14	52	46	51	38	11	85
History of								
Rheumatic fever	26	62	81	70	63	46	1	8
Subacute bacterial endocarditis	3	7	8		4	3	1	8
Systemic emboli	3	7	14	12	30	22	0	0
Initial symptoms								
Dyspnea	15	36	49	43	51	41	1	8
Fatigue	3	7	6	5	5	4	1	8
Dyspnea, fatigue	11	26	52	45	65	47	3	23
Congestive failure	1	2	0	—	0	—	8	61
Palpitation	3	7	—	—	—	—	—	
None	9	21	—		—		—	
Atrial fibrillation								
Class 1		59†		—		—		
Class 2		61‡		—		—		[illegible]
Class 3		83		78		31		[illegible]
Class 4		100		90		70		

*Age when first seen by L. B. Ellis in Group A, and age at surgery in Groups B, C, and D.
†One patient in normal rhythm, later deteriorated to Class 3 and developed atrial fibrillation.
‡Two of these patients had paroxysmal atrial fibrillation. Two others in normal rhythm later developed atrial fibrillation, one while still in Class 2 and one after deteriorating to Class 3.

carditis occurred more than twice as frequently in mitral insufficiency as in stenosis, but the difference was not statistically significant (p = 0.2).

Atrial fibrillation occurred early in the course of mitral incompetence and was almost always present when the patients were seriously disabled.

Dyspnea or a combination of dyspnea and fatigue were the usual initial complaints for the groups with insufficiency and those with stenosis. Palpitation was not a common initial complaint, although it often occurred as a secondary symptom in association with other symptoms.

A history of systemic embolization was more commonly found in patients with mitral stenosis than in those with insufficiency and the difference was significant (p = 0.02).

As judged by the ECG's (Table II), a majority of patients with mitral insufficiency had either left ventricular or combined ventricular hypertrophy, whereas patients with mitral stenosis rarely had positive evidence of left ventricular hypertrophy and frequently (47 per cent) showed right. A third of the patients with insufficiency showed no clear evidence of hypertrophy by ECG. Such a finding could mean either that no hypertrophy actually was present or that combined hypertrophy

Table II Electrocardiographic and x-ray changes

Variables		Group A Class (No. patients) 1	2	3	4	% of total patients	Group B* (%)	Group C (%)	Group D (%)
Electrocardiographic evidence of ventricular hypertrophy	None	6	5	1	1	31	34	49	15
	Left	6	10	1	3	48	35	3	77
	Right	0	2	1	1	9	13	47	0
	Combined	0	1	3	1	12	30	1	8
Roentgenographic findings									
Left atrial enlargement	+1	5	2	0	1	19	4	11	15
	+2	3	5	3	0	26	34	67	69
	+3	2	8	1	4	36	46	20	8
	+4	2	3	2	1	19	16	2	8
Ventricular enlargement	None	4	3	0	0	17	3	2	0
	Left	5	6	0	4	36	10	11	38
	Right	0	2	0	1	7	21	64	0
	Combined	3	7	6	1	40	66	23	62
Pulmonary artery prominence		Not analyzed					59	75	46
Mitral valve calcification at surgery or post mortem		Not analyzed					22	43	0

*In Group B, ECG's were analyzed in 112 patients, roentgenograms in 110.

existed and the abnormal vector forces from the enlargement of the two ventricles neutralized each other.

The roentgenographic findings were less clear-cut. Although right ventricular enlargement was diagnosed with about the same degree of frequency by this technique as by the ECG, combined ventricular enlargement was reported much more frequently by roentgenogram in the mitral insufficiency series and to a lesser degree in the mitral stenosis series. This discrepancy with the electrocardiographic findings can possibly be explained by the great degree of atrial enlargement that tended to occur in the mitral insufficiency groups. It is an obvious fact, although frequently overlooked, that when the left atrium enlarges, it not only intrudes on the posterior mediastinal space and as it becomes progressively bigger extends to the left or right, but it also pushes the rest of the heart anteriorly and rotates it in a clockwise direction so that apparent enlargement of either or both of the ventricles may be described. Thus in patients showing gross enlargement of the left atrium there is almost invariably the roentgenographic picture of both right and left ventricular enlargement even though such combined enlargement may not be evident in the ECG (Table III). This effect of atrial enlargement is apparently also evident to some extent in patients with mitral stenosis.

Table III Group A—Relationship between left atrial size and ventricular enlargement as observed at cardiac fluoroscopy and by ECG

Left atrial enlargement	None	Left	Right	Combined
Ventricular enlargement by fluoroscopy				
+1	5	3	0	0
+2	1	4	0	6
+3	1	8	2	4
+4	0	0	1	7
Ventricular enlargement by ECG				
+1	3	4	0	1
+2	4	5	2	0
+3	5	7	1	2
+4	1	4	1	2

Table IV Duration of disease in Group A patients

First seen in Class	Age when first seen	No. years in each class: Class 1	2	3	4	Total duration of known heart disease	Years followed by L. B. Ellis	Outcome
1	23	15				15	9	
	25	22	7	3		32	18	Died, pulm. ert.
	25	22				22	12	
(Average age, 40)	28	18				18	8	
	35	13	5			18	8	
	37	5	3			8	3	
	39	22	1	3		26	13	Operated
	42	24	5	1		18	7	Operated
	53	5				5	1	
	56	25	2			27	22	
	59	4				4	1	
	62	54				54	2	
2	12		10	2		12	11	Operated
	27		12			12	3	
	28	9	12	1		22	10	
(Average age 43)	33	7	32			39	14	Died, cancer
	35	18	5			23	3	
	38		30			30	3	
	39	30	10			40	9	Operated
	39		12			12	5	
	40		10	2		12	7	
	45	31	1			32	1	
	47		6			6	4	Sudden death
	48	30	7			37	4	
	49		21			21	1	Died, CHF
	52	10	5	?	2	17	6	
	59	57	1			58	1	
	61	52	1			53	1	
	63	43	6			49	2	
	72	65	1			66	1	
3	21	3	3	9		15	9	Operated
	24	9	4	11		24	9	Operated
(Average age, 36)	27		10	14		24	8	
	34	7	2	10		19	6	Died
	47			6	1	7	6	
	62	23	2	7		32	7	
4	20			8	11	19	11	Died, CHF
	47			5	9	14	4	Died
(Average age 48)	53				6	6	1	Sudden death
	54			11	3	14	3	Died
	58			8	1	9	3	Died
	59	44	?	4	4	52	4	

Enlargement of the main pulmonary artery was noted less frequently in patients with mitral insufficiency than in patients with stenosis (Table II).

Valvular calcification was significantly less common in mitral insufficiency (Table II) ($p < 0.001$), although it was seen in some patients even with pure insufficiency.

Course of the disease (Table IV). Our findings having to do with the clinical course of mitral insufficiency are based on the Group A patients. The length of [illegible] patients were stated to be in Class I [illegible]

based on the known duration of the asymptomatic phase of their heart disease, from the occurrence of rheumatic fever with cardiac involvement or the discovery of a murmur or other cardiac abnormality such as enlargement. Thus, the estimated duration of the disease in many instances must have been shorter than its actual duration.

Many patients had a remarkably long duration of known heart disease before they showed symptoms. Fifteen of the 28 patients in whom heart disease had first been recognized in an asymptomatic phase were observed in Class 1 from 22 to 65 years. If the span of years from first knowledge of heart disease to last observation is considered, 6 patients were known to have had heart disease from 49 to 66 years. Six more had had recognized disease from 31 to 40 years, 9 from 21 to 30 years, 14 from 11 to 20 years, and 7 from 4 to 10 years. Of the 12 who were first observed while in Class 1, 7 were in atrial fibrillation, 6 showed left ventricular enlargement by ECG, all showed some, and 4 showed marked or extreme atrial enlargement. After an average of seven more years of observation, 6 were still symptom free, 3 developed mild symptoms, and 3 deteriorated to Class 3, one of whom died of a pulmonary embolus and the other 2 underwent heart surgery.

Patients who were first observed with mild symptoms (Class 2) have also tended to do well. In 13 patients, the cardiac situation remained static for an observation period of 1 to 32 years (average 10 years) although 1 died of cancer and 1 underwent cardiac surgery. One patient died suddenly after 7 years of mild symptoms. Of the remaining 4, 2 have deteriorated to Class 3 after 10 and 12 years in Class 2, 1 underwent heart surgery after 2 years in Class 3, and 1 died after 2 years of congestive failure.

Patients first seen when moderately disabled in Class 3 have also fared well. In 2 patients heart disease was first diagnosed when they were in Class 2 and Class 3 respectively. Of the 6, 3 were followed for 7 to 14 years at this stage although 2 finally underwent heart surgery. One patient deteriorated after 6 years in Class 3 to Class 4 and died after a year of congestive failure.

Thus, of these 36 patients, only 4 have died a possible cardiac death, including one sudden death and one from a pulmonary embolus.

The 6 patients first seen in congestive failure (Class 4) have not done well. In 4 heart disease was first diagnosed when they were symptomatically in Class 3, and in a fifth patient knowledge of heart disease coincided with the development of congestive heart failure. Only one is alive after 4 years of failure. Five are dead, 1 after 11 years of failure, the others were in failure from 1 to 9 years.

Group D. The profile of 13 patients with ruptured chordae or papillary muscles differed in many ways from the other patients with mitral insufficiency (Tables I and II). It was mainly a disease of males (85 per cent) and they were older on the average than the other groups (average age 57 years). Four had a history of myocardial infarction 4 months to 6 years before surgery; one of these patients also had subacute bacterial endocarditis. Only one had had rheumatic fever, but in 3 other patients mild rheumatic mitral valvulitis was found at postmortem examination. In the remaining 5 the etiology was unclear. Atrial fibrillation was present in only 3, 2 of whom had rheumatic mitral insufficiency. The ECG showed left ventricular enlargement in 77 per cent of the patients and either left or combined enlargement was described in all of the patients by roentgenogram. The left atrium was only slightly to moderately enlarged in all except 2 patients. Valvular calcification did not occur. None had a history of systemic emboli.

The 2 patients who were operated while in Class 3 had symptoms for 7 months and 4 years respectively. Three patients had been in Class 3 for 6 months, 8 months, and 4 years before slipping to Class 4 for 4 to 12 months before surgery. In 8 patients the congestive failure came on abruptly and persisted for 1½ to 12 months in 7 and for 4 years in the eighth patient before surgery took place.

Discussion

It is recognized that there is a spectrum of mitral valve disturbances, ranging from pure stenosis without insufficiency through varying degrees of stenosis with insuffi

ciency to pure insufficiency. Both of these abnormalities of mitral valve function put hemodynamic strains on the heart and the circulation, but the strains differ somewhat in their nature. In mitral stenosis the pathologic physiology and the early symptomatology are clearly related to the block at the valve and often a marked increase in pulmonary vascular resistance. These abnormalities lead to increase in left atrial and pulmonary vascular pressure. They also lead to a reduction in cardiac output, especially during exercise, for reasons not entirely clear at the present time. This diminished blood flow and increase in pulmonary resistance result in the sensations of fatigue and of dyspnea which may progress so as to become incapacitating. Left ventricular failure does not occur. Failure of the right ventricle is seen late, secondary to the long-standing pulmonary hypertension.

In contrast, the severely symptomatic phase of mitral insufficiency is due to left ventricular failure resulting from the overwork of the left ventricle. Reduction in cardiac output due to reduced forward blood flow, as well as to some degree of pulmonary vascular congestion from the backflow into the left atrium, may be responsible for some early symptoms of fatigue and dyspnea before myocardial failure develops.

In the present study, patients were deliberately chosen who gave evidence of predominant mitral incompetence, in order to avoid the possibility that the clinical symptoms manifested by them were due to a stenotic lesion.

Since the symptomatology of advanced mitral insufficiency is due to left ventricular failure, the question arises: Is the failure secondary to the strain imposed by the leaking valve or is it, at least in part, due to primary myocardial failure with the valvular insufficiency of secondary importance. The latter is obviously true in patients with primary disease of the left ventricle and "functional" valvular insufficiency. It is not such patients that concern us, but those who have severe organic disturbances of the valve itself. The question of the importance of myocardial disease in such patients cannot at the present time be answered, and the relative importance of valve leak versus myocardial dam[illegible] accurately assessed except ex post facto by the results of surgery with replacement of the damaged mitral valve by a competent one. Even after such surgery the answer may not be forthcoming, because the circulation may not be restored to a completely normal hemodynamic state. This may be because the artificial valves themselves may not be hemodynamically perfect, or because such prolonged strain may have led to some irreversible physiologic and even morphologic cardiac changes, since most patients do not come to surgery until they have sustained a long-standing strain on their left ventricles. The question of a primary myocardial factor in rheumatic mitral insufficiency is not yet ruled out, however.

Although it is virtually axiomatic to assume that mitral stenosis in adult patients is always due to a preceding rheumatic fever, such an assumption cannot be made for mitral incompetence. In spite of the fact that a greater percentage of patients [illegible] this lesion have a previous history of rheumatic fever than patients with mitral stenosis, nevertheless, there are some patients in whom clearly there is an etiologic cause other than rheumatic fever. Perhaps the early appearance and the ease of recognition of the systolic murmur of mitral insufficiency (in contrast to the early missed and later developing diastolic or presystolic murmur of stenosis) are responsible for a larger number of the former patients being diagnosed as having rheumatic fever in the acute stage.

Patients in whom combined mitral stenosis and insufficiency has been proved to be present, as well as those who have organic mitral and aortic valvular disease, can be considered to be rheumatic, and this is the etiologic cause in persons coming to surgery because of dominant mitral insufficiency without other valve involvement in about 90 per cent of adult patients. A few adult patients have isolated congenital anomalies of the mitral valve such as a cleft valve with or without associated cardiac defects. A syndrome of voluminous billowing of the posterior mitral leaflet, associated with a late systolic murmur and click or "honk," has been described.[14] This may be a hereditary characteristic. Subacute bac-

teral endocarditis may cause or exacerbate insufficiency by perforating a leaflet or causing chorda rupture but this almost always occurs in a valve already damaged by rheumatic disease. The same can be said for trauma

One of the most difficult diagnostic problems is differentiating organic mitral insufficiency from a cardiomyopathy Indeed some cardiomyopathies do produce organic changes in the mitral valve and in any of them, functional insufficiency may occur as the result of left ventricular dilatation (with inadequate closure of the mitral leaflets that are held open by the relatively shortened chordae, which cause elongation of the left ventricle and displacement of the papillary muscles toward the apex) as well as by dilatation of the mitral annulus. Insufficiency can also occur in patients with left ventricular dilatation and failure of known etiology e.g hypertensive or ischemic heart disease. Careful clinical hemodynamic and angiographic assessment will usually establish whether mitral insufficiency is or is not a major factor so that patients will not inadvertently be subjected to valvular surgery In a series of 400 patients undergoing open heart surgery for mitral valve disease, there were only 3 in whom a diagnosis of cardiomyopathy was made at surgery or at post mortem examination.[11]

Coronary artery disease may lead to infarction of the papillary muscle and rupture of the muscle or attached chordae with resulting free mitral insufficiency The clinical profiles of these patients with coronary artery disease as well as those with ruptured chordae from other causes, differ strikingly as a rule from the profiles seen in cases of usual rheumatic mitral incompetence and they are often relatively easy to recognize the malignant course these patients follow should bring them to surgery promptly Our findings in regard to the clinical findings and course of these patients are in accord with those reported by others.[12]

The study which we have reported shows certain similarities in the clinical profiles of patients with severe insufficiency assumed to be of rheumatic origin, and those with mitral stenosis. The age and sex of the patients are the same. A rheumatic history occurs in half or more of the cases. Bacterial endocarditis was diagnosed in a somewhat greater number of patients with insufficiency but this may be because such endocarditis may itself produce or aggravate the leak. Systemic embolization is less common in mitral insufficiency

Strikingly different is the tendency for many patients with insufficiency to develop great enlargement of the left atrium as well as left ventricular enlargement, and these changes, together with the onset of atrial fibrillation may occur at an early or at least asymptomatic, stage of the disease. There have been numerous reports of the electrocardiographic findings in mitral insufficiency with or without associated stenosis, in which the importance of left ventricular hypertrophy as an indication of incompetence is stressed. An occasional patient with pure mitral insufficiency shows right or combined ventricular hypertrophy in the ECG [6-13]

In view of these clinical dissimilarities as well as the difference in the type of physiological strain imposed on the heart in the two conditions, is there a difference in the clinical course of the disease i e do patients with mitral insufficiency deteriorate at a more rapid rate than those with stenosis? It has been shown that patients followed from the time of their acute rheumatic fever with a diagnosis of mitral insufficiency based on the presence of an apical systolic murmur tend to follow a benign course [1 4] Other studies have shown that patients with pure or predominant mitral insufficiency do become symptomatic and ultimately die of their disease even though they may have a long latent period before serious symptoms develop [•] The occasional catastrophic progression of heart failure in patients, in which inadvertent severe rupture of the aortic leaflet of the mitral valve has been produced in the course of surgery for mitral stenosis, is well known [•] The malignant course of the disease in patients with ruptured chordae or papillary muscles has already been discussed Our study shows that patients with rheumatic mitral insufficiency who are not totally disabled may have a prolonged course under medical therapy The patients with mitral insufficiency discussed in this study are, of

course a selected group for the most part symptomatic and with well marked cardiac abnormalities We are not suggesting that patients who have mitral incompetence invariably or even frequently develop such cardiac pathology in the asymptomatic phase of their disease Rather it was our intention to study the course of disease in those patients who are thus afflicted We have not attempted to distinguish between patients who had pure mitral insufficiency with no stenosis whatsoever and those with slight stenosis. We have chosen patients in whom the essential hemodynamic fault was valvular incompetence with any stenosis that might exist playing an inconsequential role

An appreciation of the nature of the clinical course of mitral insufficiency under medical management is essential if a valid judgment is to be made as to the proper place for surgery in the relief of this condition At the present time such cardiac surgery always means open heart surgery using cardiopulmonary bypass and very frequently means valve replacement with a prosthetic device Reconstructive operations of the valve itself are now carried out mainly in special situations such as a split leaflet or possibly a ruptured chorda. Homographs and other tissue replacements are still very much in the experimental stage The early publications on surgery with valve replacement reported rather poor operative mortality figures, of the order of 20 to 25 per cent Recently the operative mortality rate has improved considerably and chance for recovery now probably approaches 5 to 10 per cent in patients not severely disabled[13] Hemodynamic and clinical improvement which often was disappointing when a large caged ball prosthesis was employed appears to be more satisfactorily obtained with the low-profile disc or lens type valve[20] Of more concern however are the number of late complications which have continued to occur Systemic embolization from valvular thrombus formation continues to be a major problem although reports have been made that full and prolonged anticoagulation with bishydroxycoumarin or allied drugs and even more strikingly the use of drugs which reduce platelet adhesiveness such as dipyridamole,[21] as well as the employment of some of the newer types of valves may reduce this hazard. Paravalvular leaks requiring operation for the relief of the recurrent insufficiency or of the hemolytic anemia which not infrequently develops in association with such leaks, occur all too often More recently evidence of deformation of the Silastic ball employed in many aortic valve replacements, occurring in a discouragingly high percentage of patients has led to an abandonment of this type of aortic valve prosthesis by many surgeons. In view of this, one should be cautious in any estimate of the permanence of the prosthetic devices now employed in the mitral area although reports of disintegration of a mitral prosthesis are rare indeed

In summary therefore, although surgery for mitral insufficiency often leads to dramatic improvement and may be life-saving, it must still be considered to be in the developmental stage Long term follow-up studies of a significantly large number of patients are not yet available and the problems attendant on late complications have not yet been surmounted. Designs of prosthetic valves are being altered and hopefully improved grafts are still experimental

It has been shown in this study that mitral insufficiency may exist in the symptom-free stage for a great many years. Many of these Class 1 patients are in atrial fibrillation and have large and even gigantic left atrial as well as ventricular enlargement usually left Physicians may become alarmed by these huge fibrillating hearts and urge surgery for their patients while they are still relatively symptom-free. Yet it has been shown that the rate of deterioration at this stage may be slow and even when symptomatic patients in Class 2 or 3 are observed the course of the disease may be remarkably static or the downward progression prolonged. Sudden death is uncommon but may occur at any stage of the disease Systemic embolization is less common than in mitral stenosis, even though the incidence of atrial fibrillation is higher In view of all these considerations it would appear that there should be no urgency about carrying out surgery in patients who have not been in congestive failure or who are not virtually completely

disabled. Cardiac enlargement by itself does not constitute an indication for surgery. Surgery should not be offered to Class 1 or 2 patients, since these patients should be able to carry on a satisfactory life and postponing surgery reduces the risk of death at operation and late complications. Such delay also may buy time while a better operation is being perfected.

Since the operative risk of Class 3 patients is substantially lower than that of Class 4 patients, and since it is likely that long-term surgical results will be better in the Class 3 patients, as they have been shown to be in similarly disabled patients with mitral stenosis surgery should *not* be postponed until a patient deteriorates into Class 4 if possible. Hence, patients in Class 3 should be given serious consideration for heart surgery.

Since the medical prognosis of Class 4 patients is poor patients with this degree of disability should be offered surgery without delay. Although the operative mortality rate is high and the degree and duration of improvement uncertain, such risks are less than the ominous outcome to be expected with medical therapy alone.

Summary

This study has been concerned chiefly with the clinical course of adult patients with predominant rheumatic mitral insufficiency under medical management. It is based on a series of 42 patients followed medically and a group of 115 patients who underwent cardiac surgery. These have been compared with a group of 138 patients proven to have pure mitral stenosis at surgery. The patients were similar in age and sex. Rheumatic fever had been diagnosed in more than half the patients with insufficiency and subacute bacterial endocarditis had occurred more frequently but a history of systemic embolism was less frequent in insufficiency than in stenosis. Strikingly different was the tendency of patients with insufficiency to develop atrial fibrillation and enlargement of the left ventricles and left atria the latter often very marked. It has been shown that mitral insufficiency may exist in the symptom free stage for many years, and many of these patients may be in atrial fibrillation and have large and even gigantic left atria and left ventricular enlargement. Deterioration may be very slow although sudden death may occur occasionally. The more malignant course and the difference in clinical profile of patients with ruptured papillary muscles or chordae tendineae is described in a group of 13 such patients.

The implications of this study in connection with the selection of patients for cardiac surgery have been discussed.

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Appraisal and reappraisal of cardiac therapy

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The management of acute dissections of the thoracic aorta

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The high mortality rate associated with acute dissections of the thoracic aorta in untreated patients reflects the life-threatening nature of this disease. Hirst and associates[1] reported 30 per cent of these patients died within 24 hours following an acute attack, 60 per cent within 2 weeks, and 90 per cent succumbed within 3 months. The principle cause of death was extension of the dissection with secondary renal artery occlusion or rupture into the pericardium, mediastinum, or thorax.

The original concept of the surgical management of dissecting aneurysms was outlined by DeBakey and associates[2] and was based on an anatomic classification of the type of dissecting aneurysm depending upon the site of origin and extent. Type 1 dissection represents an intimal tear in the ascending portion of the aorta with an extension of the dissection for a variable distance into the distal aorta and terminal branches (Fig. 1). As a consequence of proximal dissection the support of the aortic valves is often distorted, resulting in aortic insufficiency. Type 2 dissection represents a local dissection of the ascending aorta without distal extension and is more likely to be present in patients with cystic medial necrosis of the ascending aorta or Marfan's disease. Type 3, as illustrated at site *D* (Fig. 1), represents an intimal tear at, or just distal to, the origin of the left subclavian artery with a distal dissection.

Type 2 aneurysms most often occur secondary to local intrinsic disease of the aortic media and occur in the normotensive young patient. The extent and location of this lesion can be delineated by selective pulmonary angiography or aortography. Surgical correction is clearly indicated in these patients. Corrective surgery requires total cardiac bypass with isolation and inspection of the ascending aorta. It is possible to divide the aorta at the site of the intimal tear, close both the proximal and distal ends, and resuture the ascending aorta resulting in normal continuity, but resection and graft replacement is preferable to remove the degenerative aortic wall. Aortic insufficiency may result from a loss of commissural support following dissection of the intima in this area. This

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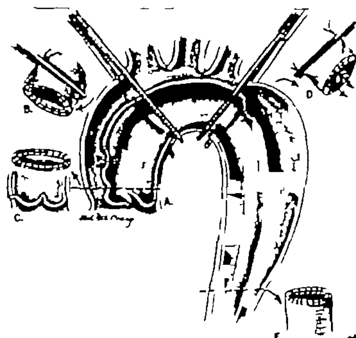


Fig 1 The surgical classification of dissecting aneurysms is based on the location, type, and extension of the disease process. *A* Type 1 An intimal tear in the ascending aorta with extension to the terminal aortic branches. *B* The distal false lumen is obliterated prior to aortic reconstruction. *C* Commissural support may be restored by suturing the dissected intima through the aortic wall *D* Type 3 An intimal tear distal to the left subclavian artery with distal dissection treated by re-entry *E*, The distal aortic false lumen is obliterated and sutured to a replacement graft prosthesis extending from site *D*

valvular lesion is progressive and left ventricular failure occurs from acute aortic insufficiency It is usually possible by evacuating the dissecting hematoma from behind the aortic valve and resuturing the commissural attachments through the aortic wall, to correct the aortic insufficiency

Type 1 and Type 3 aortic dissections most often occur in patients in the range of 55 to 75 years of age with known hypertension. The diagnosis is usually suspected clinically on the basis of the pattern of chest pain and widening of the aortic knob or a double density of the aortic region seen on the standard posterior anterior chest x-rays. It is in this group that the overall surgical results have been poor Surgical treatment of Type 1 dissections involves resection or transection of the aorta with obliteration of the false lumen or resection of the ascending aorta with replacement by a graft. Valve replacement has been required in 4 such patients in our series because of concomitant aortic insufficiency The distal dissection, Type 3, had originally been treated by creating a proximal re-entry angle but the procedure was modified to include resection of the distal aorta at the origin of dissection and replacement of the involved segment with a graft. The latter techniques require the use of left heart bypass using left atrial femoral artery or femoral venoarterial pumping to control proximal aortic hypertension and maintain renal perfusion. In 16 such patients treated, there were 4 operative deaths a surgical mortality rate of 25 per cent. The results of the surgical correction of acute and chronic dissecting aneurysms in a group of 38 patients from 1960 to 1968 reveal that the overall mortality rate was 18 of 38 patients or 47 per cent. A significant factor affecting the results of surgical repair has been the presence of uncontrolled hypertension.

Wheat and Palmer in 1965 reported on a series of patients treated with induced hypotension Their work was based on experimental observation that modifi-

tion of the forces that enhance extension of the dissection would allow tissues to heal. These forces include systolic ejection thrust and mean pulsatile aortic flow Potent antihypertensive agents are now available which can effectively cause a sustained reduction in systolic hypertension and reduce pulsatile flow thus stabilizing the aortic dissection. Induced hypotension permits control of the initial dissection and eliminates the need for emergent surgery in the critically ill, often elderly patient.

Case materials and methods

During the period July 1965 to January 1969 40 patients with acute dissections of the thoracic aorta were admitted to the Columbia Presbyterian Medical Center Twenty-seven of these patients were considered candidates for induced hypotensive therapy The criteria for selection of patients to be managed with antihypertensive agents were a systolic blood pressure of greater than 110 mm Hg and absence of significant aortic insufficiency or Marfan's disease. The patients in the hypotensive series ranged from 44 to 85 years of age.

While the presence of bloody chest fluid was considered an indication for early operation in our series we have had experience with 4 patients with evidence of intrathoracic or intrapericardial bleeding who have responded to hypotensive therapy satisfactorily An aortogram in 3 of the 27 patients revealed that the renal arteries arose from separate channels of the dissection and surgical correction would have completely isolated one kidney from the aortic flow

All patients with the presumptive diagnosis of acute dissecting aneurysms were admitted to the Thoracic Surgical Service. The most frequent cardiopulmonary catastrophe masking an acute dissection was a myocardial infarction. If the diagnosis of coronary occlusion was still in question following the examination of the patient's electrocardiogram and routine laboratory studies, a selective angiogram was carried out prior to initiation of drug therapy A venous injection through a catheter inserted into the pulmonary artery has provided an adequate outline of the disease process, and is well tolerated thus avoiding direct aortic cannulation. When the diagnosis of aortic dissection is established from routine roentgenograms, angiography is postponed until the patient's blood pressure is stabilized at a satisfactory level. Angiographic studies are carried out prior to discharge to determine the location type and extent of dissection should subsequent surgery be required.

The initial phase of therapy consists of guanethidine, 25 mg given orally chlorothiazide, 500 mg given orally and reserpine 1 mg given intravenously following an initial test dose of 0 1 mg The latter procedure precludes a hypersensitivity reaction with a subsequent hypotensive crisis. During the next 6 hours, if the systolic blood pressure does not fall to the range of 110 to 130 a catheter is placed in the radial artery to monitor arterial pressures and the patient is begun on a trimethaphan (Arfonad) drip 500 mg per 500 ml. of dextrose solution. The bed is placed at a 35 to 45 degree angle to obtain the additional effect of orthostatic hypotension. Guanethidine is increased daily until the Arfonad can be discontinued without a significant blood pressure elevation. An increased urinary output is usually noted following initiation of hypotensive therapy Ambulation is begun on the tenth to thirteenth day following institution of therapy and the patient is discharged once a satisfactory ambulatory drug regimen has been established Chest roentgenograms are obtained periodically to check for changes in the mediastinal and cardiac silhouettes.

Results

Forty patients were admitted to the Columbia Presbyterian Medical Center with acute aortic dissections. One patient died 15 minutes after entering the hospital without the benefit of therapy Of the remaining 39 patients, 27 were considered candidates for induced hypotension and 12 were treated by surgical correction. In the surgical group there were 3 operative deaths a mortality rate of 25 per cent. Of the 27 patients placed on drug therapy there were 4 deaths in the acute phase a mortality rate of 15 per cent. Eight patients with indications for surgical
tion were treated with induced h

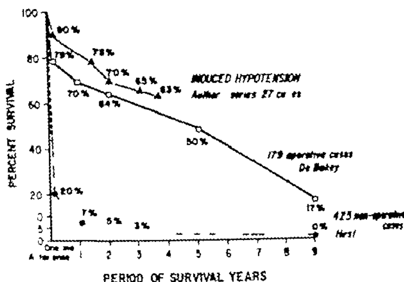


Fig 2 The follow-up for induced hypotension is comparable to late surgical results.

because of age or associated disease. Four of these 8 patients had active, leaking aneuryams two were 80 years of age and 2 had medical conditions which precluded surgical consideration Two patients had multiple abdominal and thoracic aneurysms and 2 patients required a modified drug program because of intolerance to the selected medications.

The follow up periods for induced hypotension ranged from 5 months to 3½ years. Twenty three patients survived the acute phase and 16 of these are living and well. One patient had significant widening of the aorta after 3½ years with the progressive development of aortic insufficiency This patient is scheduled for elective repair of the aortic valve and resection of the aneurysm Six patients are dead. Two of these died from rupture of abdominal aneurysms, 2 deaths were due to unrelated causes, and in one patient the cause of death was unknown. One patient died 3 months following surgery of complications related to a massive gastrointestinal hemorrhage.

Surgery therefore is reserved for patients with evidence of dissection in the absence of hypertension the presence of significant aortic insufficiency progression of the dissection with widening of the aortic shadow and continued pain or intolerance to hypotensive management.

Summary

The follow up study reveals that the selected application of induced hypotensive therapy has improved the overall long term prognosis of acute dissecting aneurysm compared to a larger operative series and to the natural history of the disease (Fig 2)[5]

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Annotations

Cigarettes, alcohol, hospitals, and atherogenesis

The wages of oral gratification have interested students of cardiovascular disease for centuries. In the case of cigarettes, earlier conjecture has been replaced by prospective epidemiologic findings in Framingham, Albany, and elsewhere, and cigarette use has been associated with markedly increased risks for the development of manifest coronary heart disease and stroke. In these investigations, however the risk of developing manifest disease has been shown to decrease rapidly among those who stop smoking, leading to the suggestion that cigarette use is related only to the acute occlusive episode, and not to the process of atherogenesis per se.[1] Habituation involving alcohol, on the other hand, has traditionally been thought to result in a protective effect upon the vessel wall, a point of view based primarily upon autopsy studies in which the vessels of chronic alcoholics have been compared with those of individuals dying from other causes (for example,[2]).

Recent reports indicating the necessity for reappraising both of these points of view have also re-emphasized the difficulties inherent in the use of hospital samples for the study of disease interrelationships. In considering the appropriateness of autopsy and other hospital samples in such investigations, three issues must be resolved.

First, when considering a possible relationship between two diseases, the investigator must acknowledge that individuals with both of the diseases in question are more likely to seek relief and become hospitalized than are individuals with but one of the diseases, simply on the basis of the burden of symptoms. The resulting overrepresentation of patients with both disorders among hospitalized patients may lead to an erroneous conclusion that the two diseases are causally related. It should be noted further that this problem is not resolved by the selection of "control" subjects from several diagnostic categories or from the general community. The second problem to be reckoned with concerns the strong selective factors which result in the performance of autopsies among only a portion of those who die. The selective biases resulting from these two mechanisms often result in erroneous conclusions which characterize only the hospital in which the study was performed, rather than the disease relationship of interest. Finally, autopsy studies usually have the further defect of being conducted in the absence of standardized antemortem historical information.

A recent report has described the relationships between cigarette and alcohol use and aortic atherosclerosis among 1,019 individuals undergoing consecutive autopsy examination at a large cancer hospital. During the course of the study the autopsy rate remained at 100 per cent, and the likelihood of sampling bias was further reduced by the demonstration that cancer and aortic atherosclerosis were not associated. In addition, all of the subjects had undergone standardized interviews concerning lifetime cigarette and alcohol use at the time of their initial admission to hospital.

No statistically significant relationship was exhibited between lifetime alcohol use and aortic atherosclerosis in this series of "social" drinkers; indeed, a very weak trend toward greater atherosclerosis severity among the heavier drinkers was noted. This finding supports the earlier contention that previous studies in this area may have inappropriately matched extremely heavy alcohol users with a comparison group which was weighted with individuals dying from cardiovascular disease.

The extent and severity of aortic atherosclerosis was statistically significantly increased among cigarette smokers, whether measured by current smoking status, intensity, or duration of cigarette use. Furthermore, former cigarette smokers were found to exhibit atherosclerosis severity intermediate between that shown by nonsmokers (and pipe and cigar smokers) on the one hand, and current cigarette smokers on the other, a finding which had been suggested by previous studies of both radiographic aortic calcification[4] and coronary atherosclerosis determined at autopsy.

A synthesis of these and earlier findings strongly suggests that not one but two partially independent causal relationships exist between the use of cigarettes and vascular disease. To the previously demonstrated short-term effects, leading to the acute manifestations of myocardial and brain infarction, now must be added the probability of more prolonged effects upon arterial walls which persist despite the cessation of cigarette use.

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Ventricular fibrillation in acute myocardial infarction

Outside intensive care areas, ventricular fibrillation (V.F.) remains an important cause of death in patients with acute myocardial infarction. It is particularly tragic that on occasion the infarct is not extensive and death is due to a sudden disturbance of rhythm rather than the hemodynamic effect of a massive myocardial infarction. As the great majority of patients with acute myocardial infarction cannot be offered the facilities of intensive care, identification is of some importance, and we have recently reviewed our experience in the Coronary Care Unit of the Royal Infirmary, Edinburgh with this point in mind. Our experience extends over 730 patients with acute myocardial infarction, 71 of these having one or more episodes of V.F.

The common classifications of V.F. are primary and secondary,[4] primary being V.F. in the absence of shock or marked circulatory failure, secondary defined as the terminal rhythm in patients dying from circulatory failure. However, our experience has led us to believe that a wider spectrum exists and the following classifications have been proposed:[5] (1) *primary*, in the patient without signs of cardiac failure and/or hypotension; (2) *complicating*, complicating pre-existing cardiac failure and/or hypotension (systolic blood pressure < 100 mm. Hg); (3) *agonal*, in patients who before the development of V.F. have already lost a vital function such as blood pressure or respiration; (4) *pacemaker induced V.F.*; (5) *drug-induced V.F.*

Our main argument with the previous definition was the failure to differentiate between V.F. complicating shock and/or cardiac failure and agonal V.F. which is preceded by the appearance of mortal signs such as loss of blood pressure and respiration. Regarding primary V.F. there is less disagreement, although some of our patients with complicating V.F. and only minimal signs of cardiac failure, e.g., persistent basal crepitations only, might have been classified as primary by other authors. Of our 71 patients, 24 had primary V.F. and 47 complicating V.F. The other types of V.F. are excluded from this annotation.

Recent observations[6] have indicated the importance of the first few hours after the onset of symptoms with regard to the risk of developing V.F. and our data confirm this. Of the 71 patients, [illegible] (54 per cent) had their first episode of V.F. within 4 hours of onset of symptoms and 50 (70 per cent) within 12 hours. This predilection for the early hours is particularly marked for patients with primary V.F. and 71 per cent of these patients had their first arrest within 4 hours. It follows that should patients be admitted within a short time of onset of symptoms then the incidence of V.F. may be comparatively high and conversely, where a unit ordinarily admits patients some time after onset of symptoms the incidence of V.F. may be low. This point is illustrated by examination of our own figures. The incidence of V.F. in patients admitted within [illegible] of onset of symptoms (12 per cent) was significantly higher than that in the group admitted after that time (3 per cent).

Much has been written about the predictability of ventricular fibrillation.[illegible] Ventricular tachycardia and frequent ventricular ectopic beats, especially of the R on T variety, have been particularly incriminated with the resultant claim that many cases of V.F. are preventable and that the incidence of V.F. in an efficient unit should be low. This has perhaps been less well emphasized is the speed with which these arrhythmias may appear and progress to V.F. In our series, when V.F. developed early in the course of myocardial infarction, it was infrequently preceded by warning arrhythmias sufficiently early to allow institution of antiarrhythmic therapy. For instance, of 12 patients who developed primary V.F. on whom adequate monitoring information was available, only 2 had premonitory arrhythmias detected and were on appropriate therapy at the time of their first arrest. It is not our purpose to de-emphasize the importance of arrhythmic harbingers and it is likely that bouts of V.F. have been prevented with appropriate prophylactic treatment, but it should be recognized that it is not always easy to predict the onset of V.F.

When V.F. occurred later in the course of myocardial infarction we found it was more predictable and 7 out of 10 patients on whom adequate monitoring information was available had had premonitory arrhythmias. Apart from arrhythmias, however, there are other possible explanations for the [illegible]

development of V.F. Late V.F. is mainly encountered in patients with continuing cardiac failure and it is possible that diuretic therapy and electrolytic upset are sometimes responsible. In addition, Wallace[24] has reported a rise in urinary catecholamines at the time of discharge from hospital and this observation may be relevant to the occurrence of V.F. on the day of discharge from the hospital which we, and others, have observed. Finally, and we feel this is probably the most important aspect, the late occurrence of V.F. may be the initial manifestation of fresh infarction.[12-16] Three of our patients in the group had necropsies performed and in 2 there was evidence of fresh infarction.

An earlier report[4] suggested that V.F. was particularly common in young male patients. We found no difference in incidence between the sexes, and the difference in incidence in patients under 50 years of age (11 per cent), compared with that in those between 50 and 69 years of age (8 per cent), was not statistically significant. Nonetheless, it should be noted that the impact on mortality rates is maximal in the younger age groups, as it is from this group that the best chance of survival exists. Thus 11 of the 15 patients less than 50 years of age survived to leave hospital while only 22 of the 56 patients over 50 did likewise. The natural tendency to report successful instances probably accounts for the apparent increased incidence of V.F. in younger patients. The site of infarction, the clinical condition of the patient at the time of admission to the hospital, and the results of serum enzyme estimations were of no help in predicting patients liable to develop V.F.

Can therapy be given to all patients when first seen which will prevent V.F.? The development of safe and potent antiarrhythmic regime is one of the chief aims and, although lidocaine can undoubtedly suppress ventricular arrhythmias, there is as yet no good evidence that it will prevent V.F. in the early stages of myocardial infarction. It is possible that this question will be answered shortly as increasing use of lidocaine in the early hours of infarction is encouraged. Regarding the therapy of V.F. itself there is now no doubt that the treatment of choice is immediate defibrillation. In our unit this is normally accomplished within 1 minute, and with this policy defibrillation has been almost always successful in restoring sinus rhythm except in those patients with cardiogenic shock or with signs of frank pulmonary edema. It is only in those patients that recourse to external cardiac massage and intubation has been necessary. The clinical condition of the patient at the time of the arrest was of prime importance in determining whether the patient left hospital alive. As others[8-10] have reported, the chances of survival following primary V.F. were good and 20 of 24 such patients left the hospital alive. The figures for complicating V.F. were not as good and subdividing this group into 3 categories according to the clinical signs of cardiac failure, the figures ranged from 8 of 14 patients with basal crepitations alone, to no survivors of 17 patients with cardiogenic shock or pulmonary edema, with 5 survivors in an intermediate group of 16 patients. Doubt exists in regard to long-term prospects of these patients who leave hospital.[25] Our period of follow-up varies from 2 years to 9 months and over this period 6 of the 33 patients have died. Only 1 of the 20 patients leaving the hospital after primary V.F. has since died suggesting that these patients may not be particularly prone to sudden death following discharge from the hospital.

In conclusion, I must admit that our attempts to identify patients liable to V.F. and particularly primary V.F. have been largely unsuccessful, as we found that many patients developed the arrhythmia abruptly and with little warning. It is true that the majority who developed V.F. at a later stage had prior arrhythmias, but identification of this group is unlikely to make any great impact on mortality rates as V.F. after 48 hours is comparatively uncommon. It follows that we must continue to search for means of identifying the early group, for they constitute by far the majority of patients developing V.F. The natural history of V.F., however, affords little time once infarction has occurred, and for this reason one area which should receive attention is the care of the ambulatory patient with coronary artery disease before the development of infarction.

I should like to thank the medical and nursing staff of the Coronary Care Unit, Royal Infirmary, Edinburgh, and particularly Professor K. W. Donald, Dr. D. G. Julian, and Dr. M. F. Oliver for their helpful criticism during preparation of this annotation.

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There is such an entity as a cardiac invalid

The cardiologist and especially the general practitioner and general internist often fail to recognize that a patient with severe heart disease can be an invalid—just as much an invalid as a paraplegic or other patient with a severe physical disability. Unfortunately, physicians fail to realize that, in spite of the best medical care, the cardiac state can become so advanced that the cardiac reserve is reduced to the point that the patient must live in bed or a wheel chair. Regardless of opinions, such a state does exist. When this advanced state of reduced cardiac reserve becomes more generally recognized, therapeutic management will be more satisfactory. True, such a state should not be accepted as final, but until cardiac transplantation is entirely satisfactory, therapy will be better if such a state is recognized. Research for the purpose of improving the management of the patient with minimal cardiac reserve should continue to be supported. However, such a state of invalidism will probably exist forever in one form or another.

It is difficult and unpleasant for the physician to inform his patient that he must live in bed and/or a chair. Indeed, initially, at least, the patient should be told that improvement will be very slow with invalid-type management. Once the patient and physician have accepted the fact that the patient is a cardiac invalid, therapy should be outlined accordingly. By means of a good psychologic and philosophic approach, along with other medical and financial assistance when necessary, much can be done to produce a happy patient who can live many more months or years in considerable comfort in spite of markedly reduced cardiac reserve. The attitude of the patient and his acceptance of the invalid state and existence depend to an extremely large extent upon the attitude of his cardiologist and general physician as well as his family and associates.

There is a need to educate the public in this regard and to develop facilities for the convenience of the patient to make life pleasant and happy at home as well as in the hospital. Unfortunately, society in general is not fully aware of this long-existing problem of the cardiac cripple. The physician should guide the way for maximal use of social services in his community toward the development of facilities for the management of cardiac invalids in which special therapeutic and nursing requirements can be met. It will be a long time before a heart can be satisfactorily replaced, and even then donors of healthy hearts will be limited in number. Therefore, the invalid cardiac state deserves serious consideration. It is remarkable what can be accomplished for these patients with absolute bed rest for long periods of time. Rest in bed and/or a wheel chair reduces the demands on the heart to a level which can be provided by the cardiac reserve.

Most if not all cardiologists have at least a few invalid cardiac patients under their care. Unfortunately, the attitude and approach are concerned with "curing" these patients, whereas it is actually impossible to do so at present. Also, in a [illegible] to provide early ambulation or a cure, the patient's death is often hastened, preceded by much suffering. The physician should constantly [illegible] evaluate the state of his patient. The decision whether or not to permit limited activity is a [illegible] of experience and judgment. However, resumption of any activity after a prolonged period of bed rest must always be slow, graded, meticulously timed, and carefully supervised.

The invalid cardiac state does exist. Let us do everything possible in the interest of life and happiness for the patient and his family.

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Renal scars and pyelonephritis

Thirty years ago Weiss and Parker[1] introduced American medicine to pyelonephritis, condition already well studied in Europe. With enthusiasm for the diagnosis increasing over the years and consultation of the original reports concomitantly apparently decreasing, state has been reached which calls for clarification of anatomic criteria.

One source of error probably has been the common practice of reading only summaries and not also the bodies of published papers. Weiss and Parker summary paragraph 6, gives four main morphologic characteristics, largely in the cortex, in chronic and in healed pyelonephritis, astonishingly omitting a fifth, perhaps even more important series of alterations described earlier in the paper—changes in the renal pelvis.

The chronic form of pyelonephritis was described as follows: "The wall of the pelvis is thickened owing to increased connective tissue which is markedly infiltrated with lymphocytes, plasma cells and polymorphonuclear leukocytes. In addition there may be newly formed lymphoid nodules with germinal centers. The pelvic epithelium may be covered with an exudate of fibrin and leukocytes or may be absent as result of erosion or ulceration."[1]

Healed pyelonephritis was summarized as follows: "The wall of the pelvis is thickened owing to increase in connective tissue and is infiltrated with lymphocytes and plasma cells. In some instances there may be formation of lymphoid nodules with active germinal centers."[1]

Thanks to the summary' omission of pelvic changes and its mention of largely cortical alterations, there is now virtually no attention paid to pelvis and medulla. The term, pyelonephritis, either present or past, is applied to every gross cortical *scar especially if it is viewed as nonpyramidal*. Microscopically there is unquestioning application of the sixth paragraph of the summary: In chronic and healed pyelonephritis the main morphologic characteristics consist in ( ) the inflammatory reaction of the interstitial tissues (b) colloid casts in the tubules, which are lined with trophic epithelium (c) periglomerular fibrosis (d) evidence of infection or inflammation in the tubules."[1]

Reference to the text of Weiss and Parker indicates how abbreviated is their summary. Interstitial lymphocytic infiltration has, for example, been used to satisfy criterion ( ), yet the text clearly states such infiltration marks V-shaped vascular scars; the additional presence of plasma cells and occasionally of eosinophiles characterizes interstitial infiltration of chronic or of healed pyelonephritis in scars which are U-shaped. The body of the paper further says, "The vascular scars and infiltrates are confined to the cortex, while in pyelonephritis they extend into the *pyramids and calyces* (SMR italics).

Criterion (b), *colloid casts in the tubules*, especially has been trouble-maker because it is so readily identifiable and hence applicable, as is criterion ( ), periglomerular fibrosis. Parenthetically criterion (d) is usually gallantly disregarded. A recent example[2] illustrates the dangers inherent in failing to apply all criteria—changes in cortex and in medulla and in pelvis.

In a 44-year-old woman dying of uremia, the kidneys showed interstitial inflammatory reaction (lymphocytes and some plasma cells), periglomerular fibrosis, and trophic tubules with colloid-like casts. Discussing the case, the guest pathologist[3] remarked: In short, the composite histologic picture was compatible with a diagnosis of chronic pyelonephritis. The old criteria of Weiss and Parker—thyroidization, periglomerular fibrosis and an interstitial inflammatory infiltrate—were observed. H did not mention the two other criteria of those authors, namely evidence of infection or inflammation in the tubules and pelvic disturbances. The pathologist went on to break down what, on original standards, already was an erroneous diagnosis. The cortical changes in the case at point were attributed to renal artery stenosis at its origin, and he termed the disturbance "interstitial nephritis" an appellation with which it is difficult to quarrel.

When one thinks of the undoubtedly numerous subclinical derangements to which the human body is subject through its life, it should not be astonishing that the various organs, the kidney included, demonstrate nonspecific anatomic stigmata. Among the latter common one perhaps best deserves the noncommittal term, "interstitial nephritis." Also, we would be spared the contrived explanation for the absence of bacteriuria in the presence of what is falsely called pyelonephritis. It might also result in questioning the too ready attribution of hypertension to what is erroneously described as "chronic pyelonephritis."

Marshall[4] has *attempted to halt the rush to apply* the diagnoses of chronic pyelonephritis as well as that of arterial ischemia to combination of little cysts and focal depressions in the kidney of adults. These, he believes, originate in localized abnormalities already present in 35 per cent of routine necropsies of babies less than one month old.

In an attempt to confirm Marshall' findings, I reviewed the routine macroscopic kidney section of 60 autopsies done in single year (1955) on stillborn fetuses in varied stages of development (1,200 to 3,800 grams) and on live-births surviving as long as 6 months. A few fetuses under 1,500 grams showed isolated, very small areas at the cortical surface which were composed virtually entirely of stroma, apparently evanescent, because such changes were not seen in later stages of maturation. Of the relatively mature stillborn fetuses, 4 of 15 showed one, rarely two, small foci in which glomerules, uncommonly two had a dilated or cystic capsular space, usually containing hypoplastic tuft unit. Of those babies *surviving* birth, 11 of 18 had the glomerular disturbances. Thus, of 33 cases weighing 2,500 grams or more, 15 or 45 per cent evinced the changes described by Marshall. A few

had single tiny nests of tubular dilatation or cyst formation, thus suggesting that cortical cysts, seen in adult life may have their origin during fetal development, either from a glomerulus or tubule.

Marshall also points to "vascular sinusoids" as being associated with the localized renal malformation. Only in few cases did I see such blood-filled dilated channels, but these were present only in areas where tubules were few or missing and glomeruli were usually lacking

In summary adherence to all five criteria of pyelonephritis described by Weiss and Parker should restore degree of order in categorizing renal lesions, assisted by knowledge of Marshall findings.

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Letter to the Editor

Hematocrit after acute myocardial infarction

To the Editor:

I have read with some interest the discussion in the letters to the Editor on this subject. Both letters in the May 1969 issue (Vol. 77 No. 5) seem to be beating a dead horse to death.

We have found that there is a very frequent relationship of the hematocrit to blood velocity by using an ultralow frequency ballistocardiograph, which shows an amplitude relationship to the velocity of blood flow (*Aerospace Medicine* November 1967 and March 1969). The abnormal ballistocardiogram in which a follow-up showed high risk and eventual death over a three year period showed rise in the hematocrit. This takes place in a majority of people who show inotropic changes in the myocardium as manifested in the ballistocardiogram. This would make sense, since in the overall picture of the oxygen transport system, one would expect an increase in hematocrit to compensate for the lower velocity of blood flow.

I would expect the hematocrit to be increased in these people who have suffered further insult to the myocardium and its resulting inability to accelerate blood forcefully. Dintenfass (*The Medical Journal of Australia* April 20, 1968) has shown that the viscosity of blood is related to flow velocity and has also shown that blood viscosity is four, five, and rarely ten times higher in patients suffering from coronary occlusions. Subsequent studies confirm that great elevation of blood viscosity may be observed in patients suffering from coronary heart disease. He has also shown a relationship of the velocity gradient to blood viscosity and clotting of blood.

The scope for research in this field is enormous, and until cardiovascular research can cure itself of the neurosis of pressure measurement, and think in terms of the velocity of flow, the understanding of these mechanisms will remain obscure.

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Book reviews

COLLATERAL CIRCULATION IN CLINICAL SURGERY. Edited by D. E. Strandness, Jr., M.D. Philadelphia, 1969, W. B. Saunders Company. 633 pages. Price $18.50.

This is an important subject in medicine. It certainly needs more careful and sound scientific attention. Dr. Strandness has produced a very useful book, which summarizes very well the present state of knowledge concerning the collateral circulation for every organ of the body and the limbs. He was assisted by eight contributors most of them from Seattle. They are all surgeons and, therefore, the surgical approach is emphasized. Consideration of the collateral circulation is much neglected in clinical medicine. Unfortunately, contributions from physiologists, pharmacologists, and physicians were not included in this monograph. Nevertheless, this is a very useful book on an extremely important subject by an author who has been contributing significantly to cardiovascular surgery and physiology.

ABNORMAL ARTERIOVENOUS COMMUNICATIONS. Peripheral and Intracardiac, Acquired and Congenital. By Emile Holman, M.D. Springfield, Ill., 1968, Charles C Thomas, Publisher. 243 pages. Price $16.50.

Emile Holman has been interested in A-V communications for many years and has made many important contributions to this clinical entity as indicated by some of his own publications listed in the references at the end of the monograph. Incidentally, this is a good list of references. This monograph summarizes the clinical and surgical management of A-V communications very nicely. The monograph summarizes Dr. Holman's present opinions concerning the problems related to A-V communications. The text is clearly written and the illustrations are very good. All vascular surgeons should own this book and many surgeons in training in cardiovascular surgery will find this monograph helpful. This is a good book by one of the surgical pioneers in the field.

MEDICINE TODAY. Vol. 2, Nos. 8 and 9. Edited by Rohinton B. Khambatta, Karachi, Pakistan, 1968, 238 pages.

This special issue of *Medicine Today* published in Pakistan is dedicated to Dr. Paul Dudley White and is concerned with ischemic heart disease. Readers of this section of the AMERICAN HEART JOURNAL should know of the issue since they may wish to own a copy or at least read this fine publication. The contributors are a few of Dr. White's many friends who present papers on selected aspects of ischemic heart disease.

YEAR BOOK OF CARDIOVASCULAR MEDICINE AND SURGERY. Edited by Eugene Braunwald, M.D., Proctor Harvey, M.D., John W. Kirklin, M.D., Alexander S. Nadas, M.D., Oglesby Paul, M.D., Robert W. Wilkins, M.D., and Irving S. Wright, M.D. Chicago, 1968, Year Book Medical Publishers, Inc., 459 pages. Price $10.00.

This annual review of cardiovascular medicine is of the usual format. It is a good volume to use by those who do not follow the medical literature closely. Unfortunately, for those who must depend upon such books, the volume consists of highly selected papers. The publications of some authors are rather extensively covered whereas papers of others are ignored, including those of Christian Barnard. Furthermore, as in any summary of this nature, the details of the studies are not included. This book is probably advantageous for the busy physician who must depend upon the judgment of the editors who are responsible for the selection of subject, concepts, and authors for inclusion in the volume. The volume is consistent with the quality of past year books which continue to serve a purpose. The subject and author indices are good.

RESPONSES TO EXERCISE AFTER BED REST AND AFTER TRAINING. By Bengt Saltin, M.D., Gunnar Blomqvist, M.D., Jere H. Mitchell, M.D., Robert L. Johnson, Jr., M.D., Kern Wildenthal, M.D., and Carleton B. Chapman, M.D., American Heart Association Monograph No. 23, New York, 1968, The American Heart Association, Inc., 78 pages. Price $4.00.

This is a special bound monograph of a paper which appeared in *Circulation*, November 1968, as Supplement VII. The volume summarizes the studies of Saltin and associates. Those who do not subscribe to *Circulation* may purchase this volume from the American Heart Association. The monograph summarizes the experiments of Saltin and his associates on a very difficult physiologic problem: rest and exercise.

Books received

BIOMECHANICS—MEDICINE AND SPORT, Vol. 2, Technique of Drawings of Movement and Movement Analysis. By J. Wartenweiler, E. Jokl, and M. Hebbelinck, Basel, 1968, S. Karger AG, [illegible] pages. Price $19.20.

COMPREHENSIVE CARDIAC CARE. By Kathleen G. Andreoli, Virginia K. Hunn, Douglas P. Zipes, and Andrew G. Wallace, St. Louis, 1968, The C. V. Mosby Company. 153 pages. Price $5.25.

Mecanismos que intervienen en la Hipertension Portal. By Hector Orrego Matte, Santiago, 1968 Universidad de Chile, 132 pages.

Modern Treatment September 1968, Vol. 5 No. 5 1 Treatment of Common Allergic Problems By Roy Patterson. 2 Rehabilitation Edited by Daniel J Feldman, New York, 1968 Paul B Hoeber Inc., Medical Division, Harper & Row Publishers, 1,500 pages Price $16.00 per year

Oxygen Transport in Blood and Tissue. Edited by D W Lubbers, U C. Luft, G Thews, and E Witzleb, Stuttgart, 1968, Georg Thieme Verlag 284 pages Price $8.75.

A Practice of Cardiac Catheterization By David Mendel, Philadelphia and Oxford, 1968, F A Davis Company and Blackwell Scientific Publications 362 pages, Price $12.25.

Serotonin By Irvine H Page, Chicago, 1968, Year Book Medical Publishers Inc., 142 pages, Price $7.95

Advances in Cardiopulmonary Diseases—Vol IV 1969 Edited by Andrew L. Banyai and Benjamin L. Cohen, Chicago, 1969 Year Book Medical Publishers Inc., 331 pages, Price $13.95.

Epidemiologie van Ischaemische Hartaandoeningen (Epidemiology of Ischaemic Heart Disease). By M. K. DeSoto-Hartgrink, Groningen, Netherlands, 1968, Nederlands Instituut voor Praeventieve Geneeskunde TNO Wolters-Noordhoff n.v. 125 pages.

Anesthesia, Resuscitation and Intensive Care By Walter Norris and Donald Campbell, Baltimore, 1968, Williams & Wilkins Company 271 pages. Price $5.00.

1969 Current Therapy By Howard F Conn, Philadelphia 1969 W B Saunders Company 945 pages Price $15.00

Die Kardioversion By Martin Friedemann, Stuttgart 1968 Verlag Hans Huber Bern, 163 pages

Medical Subjects U—ATA Handbook No 63 Vol. 3 Medical Stamps By F Wills Hamden Milwaukee, 1968, American Topical Association, Inc 87 pages Price $5.00

Modern Treatment November 1968 Vol 5 No 6 1 Treatment of P... By Richard I H Wang 2 Treatment of Neuropathies By Robert J Joynt, New York, November 1968 Paul B Hoeber Inc Medical Division, Harper & Row Publishers, 1,500 pages Price $16.00 per year

Modern Treatment January 1969 Vol 6 No 1 1 Treatment of Restrictive Pulmonary Insufficiency By Edwin Rayner Levine 2 Treatment of Liver Disease By Fenton Schaffner New York, January 1969 Paul B Hoeber Inc Medical Division, Harper & Row Publishers, 1,600 pages Price $16.00 per year

Announcements

Seventh Annual Cardiology Seminar on Arrhythmias and Related Topics, sponsored by the Rogers Heart Foundation, will take place at the Tides Bath Club Redington Beach Fla., Oct. 23 through 26 1969 The visiting faculty include Stephen M A res, St Vincent Hospital and Medical Center New York N Y J Willis Hurst, Emory University School of Medicine Atlanta Ga. David P La ler Peter Bent Brigham Hospital, Boston, Mass. R shid A Massum D C. General Hospital, Washington D C Jane Somerville Institute of Cardiology London England Bernard Tabatznik, Sinai Hospital Baltimore, Md and Andrew G Wallace, Duke University Medical Center Durham N C The seminar will be directed by Henry J L Marriott St Petersburg Fla For further details write the Rogers Heart Foundation St Anthony Hospital St. Petersburg Fla

A Course in Interpretation of Complex Arrhythmias will be given at Michael Reese Hospital and Medical Center by Alfred Pick M D Richard Langendorf M D and Louis N Katz, M D This is a advanced course intended only for experienced electrocardiographer The class will meet daily from 9 00 A.M. to 5:00 P.M. Dec 8 through 13 1969 Registration is limited t 30 The tuition fee is $150 00

Further information and a copy of the lecture schedule may be obtained from the administrative assistant, Cardiovascular Institute, Michael Reese Hospital and Medical Center 29th Street and Ellis Avenue, Chicago, Ill. 60616

Eighth Annual Jane Nugent Cochems Competition The University of Colorado School of Medicine announces the Eighth Annual Cochems Competition with a prize of $2 500 to be awarded to the author of the best paper in the field of "Thrombophlebitis and Basic Vascular Problems. Basic vascular problems under consideration in this instance should be concerned with the underlying mechanism or processes of vascular disease, particularly those associated with thrombosis, but *not necessarily restricted to it.* All persons holding the doctorate degree and who are subject to U S. income tax are eligible Entries must be received in triplicate including all charts, illustrations, and photographs on or before Nov 15 1969 The judges appointed by the Dean are Dr Sol Sherry Professor and Chairman of the Department of Medicine, Temple University School of Medicine and Dr Michael E. DeBakey Professor and Head of the Department of Surgery Baylor University College of Medicine. Decisions of the judges are final and they may elect at their discretion not to award the prize.

Papers submitted in the competition may not be published until after the winner has been announced early in 1970. The winning paper, if published, must carry the designation, A ward the Jane Nugent Cochems *Prize.*

Inquiries regarding the competition and manuscripts should be submitted to Dr John J Conger Vice-President for Medical Affairs, University of Colorado Medical Center 4200 E. Ninth Ave. Denver Colo. 80220.

A Conference on Stroke will be held Sept. 8 to 20 1969 at the Pick Nicollet Hotel in Minneapolis Minn. The conference is sponsored by the American Rehabilitation Foundation under a grant from the Social and Rehabilitation Services, United States Department of Health, Education, and Welfare. The fee will be 20 dollars registration open to all disciplines. Contact Dr Thomas P Anderson American Rehabilitation Foundation, 1800 Chicago Ave., Minneapolis, Minn. 55404.

The Second Conference on Experimental Medicine and Surgery in Primates will be held Sept. 7 to 12 1969 sponsored by the New York University School of Medicine. For further information contact the Conference co-chairmen Edward I Goldsmith M D., The New York Cornell Medical Center 525 E. 68th St., New York N Y 10021 J Moor Jankowski, M D., New York University Medical Center 550 First Ave New York, N Y 10016. The Conference Coordinator is Robert G McRitchie, Ph.D New York University School of Medicine.

VII International Congress of Angiology of the International Union of Angiology Liège, Belgium Sept. 1 through 5, 1970.

The officers are President, Professor F Olin [illegible] Vice-President, Professor D [illegible] (Liège) Secretary General, Dr J Lambert [illegible] (Liège) Secretary General, Dr J Lambert [illegible] technical organization by Belgian Organizing Centre, 15 Boulevard de l'Empereur Brussels 1 Belgium Telephone 02 11.62.48. Cable: Bedel Brussels.

All queries concerning the scientific organization (symposia, round tables, communications, and scientific exhibition) should be sent to: VII International Congress of Angiology 59 Boulevard de la Constitution Liège, Belgium.

American Heart Journal

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Editorial

Hypotensive drug therapy in the management of hypertension

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The availability of a wide spectrum of potent hypotensive drugs during the past 20 years has led to their widespread use in an attempt to modify the adverse effects of systemic arterial hypertension.

The purpose of this paper is to critically evaluate these hypotensive drugs in terms of effectiveness, method of usage, and adverse reaction and thereby to place in some perspective the medical therapy of hypertension.

The hypotensive agents commonly employed today include reserpine, hydrochlorothiazide, methyldopa, pargyline, Aldactone A, hydralazine, and guanethidine.

Reserpine exerts its effect by depleting the adrenergic nerve of noradrenaline by increasing its free storage in the nerve ending where it subsequently undergoes degradation. Hydrochlorothiazide reduces blood volume and acts as a natriuretic agent. Its long term effects may depend on a reduction in the salt and water content of the arteriolar wall. Methyldopa blocks the enzymatic degradation of tyrosine to noradrenaline; pargyline is a monoamine oxidase inhibitor, and Aldactone A is an aldosterone antagonist which interferes with sodium-potassium interchange in the distal tubule of the kidney. The action of hydralazine is not well understood but it may act via a renal or hypothalamic mechanism. Guanethidine blocks the release of noradrenaline from the adrenergic nerves by increasing its granular storage; however, its mechanism of hypotensive activity appears to be related more to reduction of cardiac output than to its peripheral action.

The effect of lowering of the arterial blood pressure upon the morbidity and mortality of hypertension

It has become evident that successful lowering of the blood pressure will reduce the morbidity and the mortality rate resulting from hypertensive disease and will permit longer life and lesser incidence of heart failure, strokes, and uremia. These facts have been particularly emphasized by the changes which have occurred in the evolution of the most serious form of hypertensive disease, namely, malignant hypertension. Whereas during the era preceding the availability of currently employed therapeutic agents death often occurred in a matter of months, today many treated patients can look forward to long and productive lives, particularly when treatment is started early and before renal impairment becomes too severe. Recently, Mawar and co-workers re-

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ported the eleven year survival of a patient with malignant hypertension treated with a combination of hypotensive agents. This author[8] has also recently reported a similar case with a fourteen year survival from the onset of severe malignant hypertension This patient is still alive and well on relatively small doses of guanethidine methyldopa and hydrochlorothiazide.

A number of control placebo periods during which the hypotensive drugs were stopped or seriously curtailed in this latter case impressed upon us the rapidity and virulence with which a very high systemic arterial pressure can produce deterioration as manifested by severe headaches, visual disturbances, worsening of the fundi left ventricular failure etc In our hypertension clinic we have also been impressed with the rarity of new cases of malignant hypertension since the increased use of effective hypotensive agents. The occasional case that does present itself today is almost always an untreated or poorly treated patient This has been the experience in many hypertensive clinics throughout the country

In a group of 36 moderately severe hypertensive patients followed in our hypertension clinic during the past 16 years on a program of combined drug therapy we have not seen any cases of cerebrovascular accident or pulmonary edema While mild renal impairment was evident in many there have been no cases of uremia However two myocardial infarcts have occurred in this group

Who should be treated and the choice of drugs

Prior to initiating treatment of hypertension with drugs a number of procedures are necessary First one should attempt to evaluate not only the casual blood pressure reading but also attempt to obtain more basal readings by having the patient lie quietly in a room for 20 to 30 minutes and by repeating many individual blood pressure readings without talking to the patient. One must also evaluate the severity of the hypertension in terms of the fundi the ECG the heart size on a six foot x-ray film and if possible renal function tests such as creatinine clearance. The patient who has had severe or significant hypertension even of relatively short duration may already show changes in several of the above parameters which indicate to the physician the need for treatment as well as the degree of treatment necessary One must also perform investigations to rule out secondary or surgically correctable causes of hypertension, but this is beyond the scope of this article except to stress the importance of base line study of the electrolytes and the CO_2 combining power prior to initiating drug therapy

After having completed the above assessment, one can then arbitrarily divide the hypertensive patients into one of four groups and on this basis arrive at a systematic approach to treatment *Group A* mild constant hypertension, otherwise normal *Group B* moderate hypertension, diastolic blood pressure usually 110 mm. Hg or higher plus evidence of left ventricular enlargement and fundal changes *Group C* severe hypertension diastolic blood pressure usually 120 mm. Hg or higher a more severe degree of left ventricular enlargement and fundal changes usually Grade II or Grade III (Keith-Wagener) *Group D* malignant hypertension.

Group A All Group A cases should be placed on a salt restriction and weight reduction diet as well as an exercise program and should be given sedation where necessary In addition male patients under 60 who do not respond to the above regimen should be placed on mild drug therapy such as 25 mg of hydrochlorothiazide several times a week. While any decision to use drugs in this group may be somewhat arbitrary the physician who decides to use them may do so with some assurance since insurance actuarial tables reveal an increased mortality rate with even mild consistent elevation of systolic blood pressure.

Group B In this group, a combination of 0 1 mg of reserpine and 25 to 50 mg. of hydrochlorothiazide daily may prove quite effective. The serum potassium should be checked at regular intervals and if it is consistently below 3.5 mEq. per liter on the above regimen a supplement of elixir potassium chloride should be added At least one third of the patients on long-

term thiazide therapy will develop asymptomatic hypokalemia. Other therapeutic alternatives in Group B patients include a daily combination of 250 to 500 mg of methyldopa and 25 mg of hydrochlorothiazide or a combination of Aldactone-A 25 mg plus 25 to 50 mg of hydrochlorothiazide. This latter combination has the advantage of conserving potassium by decreasing the sodium potassium exchange in the distal tubules of the kidney Since many patients may become depressed or slow up on even very small doses of reserpine the other alternative form of therapy may be used quite frequently Guanethidine is usually not necessary in this group

Group C These patients represent the advanced hypertensive group and are the ones most likely to develop serious complications. Therapy is started as in Group B using combinations of reserpine and thiazides, methyldopa and thiazides, or Aldactone-A and thiazides. Guanethidine is gradually added starting with x mg b.i.d. and increasing by x mg increments until the standing blood pressure is reduced to near normal levels. The closer one approaches to normal the greater the risk of fainting or severe postural hypotension and in many cases one may settle for a slightly higher standing blood pressure in order to ensure a more comfortable existence. Six inch blocks can be placed under the head of the bed at night or the head of the bed can be raised by using pillows. In this way one takes advantage of the striking postural effects of guanethidine. One can also progressively increase the dose of methyldopa up to 1 2 or even 3 Gm per day This latter drug may also produce postural hypotension and all these patients in Group C should have their blood pressures taken in the lying sitting and standing positions t frequent intervals. One may also add Aldactone-A in increasing increments, but two tablets daily is usually enough since this drug is not a potent hypotensive agent It will however prevent hypokalemia otherwise supplements of potassium chloride may have to be supplied

In some cases with renal impairment one may choose to add hydralazine (Apresoline) since this drug and alpha methyldopa are the only two which increase the renal plasma flow

Group D These are the patients with malignant hypertension and this condition should be regarded as a medical emergency Parenteral therapy should be started immediately and a number of agents can be used Intravenous Diazoxide, 300 mg can be given at intervals but this drug is still not available for general use Intravenous Arfonad 500 mg in 500 c.c. of dextrose and water can be administered slowly This rapidly acting ganglion blocking agent is brief in its duration of action but fairly effective. Guanethidine 0.25 mg per kilogram of body weight administered subcutaneously intramuscular reserpine and intramuscular hydralazine as well as intravenous furosemide 40 mg represent other available choices. In this author's experience, a combination of intramuscular reserpine (except where the sensorium is clouded) 1 mg followed by 2 to 5 mg every 6 to 8 hours plus intramuscular hydralazine 10 to 20 mg repeated at 8 hour intervals if necessary is a very good starting combination. One adds oral hypotensive agents as outlined under Group C in a gradual and progressive fashion switching completely in 24 to 72 hours if possible from parenteral to oral medication It should be noted that phentothiazine tranquilizers may interfere with the effectiveness of guanethidine.

Adverse and side effects of hypotensive drugs

Whereas the availability of powerful combinations of hypotensive medications has probably altered the course of hypertensive cardiovascular disease by diminishing some of the more serious complications which resulted in serious morbidity and an increased mortality rate, the drugs which are used have many side effects and these must be balanced against the expected benefits of treatment in each individual case

Reserpine can produce serious mental depression and certainly slow up many patients. It increases the risk of heart block in patients with conduction defects and increases the frequency of duodenal ulcers. It should always be used in small doses, not more than 0 5 mg per day

Many physicians prefer to omit reserpine and make one of the thiazides the basic unit of therapy Thiazides can produce hyperglycemia and hyperuricemia and in some cases tolbutamide and allopurinol may have to be added to the regimen Hypokalemia occurs in more than one *third of the patients to whom it is administered* Hydralazine may produce tachycardia arthritis, and lupus erythematosus disseminata It does however increase renal plasma flow and if utilized should be used in doses below 200 mg per day Aldactone-A may cause nausea and vomiting as well as hyperkalemia in uremic patients Methyldopa can produce drowsiness and fatigue initially as well as a positive Coombs test and occasional cases of hemolytic anemia and lupus. In this au*thor s experience these latter complications* are rare and during a rather extensive use of this drug over the past three years only one case of hemolytic anemia has been encountered Guanethidine may produce difficulties with ejaculation as well as diarrhea. Sudden syncope may occur as a result of postural hypotension Pargyline can lead to hypertensive crises if certain cheeses rich in tyramine are eaten while taking this drug A knowledge of side effects, a cautious use of these drugs with a slow increase in the increments of dosage and the use of combined therapy permits an effective hypotensive program with a minimum of adverse reactions.

Summary

The availability of powerful hypotensive drugs has made possible effective and consistent lowering of the systemic arterial blood pressure. This in turn has led to a *diminution in the incidence of serious com*plications which result in the death and morbidity of hypertensive patients.

Each patient should be carefully evaluated according to the criteria set down above and classified in terms of the severity and state of his illness. Such a classification permits an intelligent and individual approach to therapy and tends to initiate an appropriate form of treat*ment at a relatively early stage in the* evolution of hypertensive vascular disease

Treatment with combinations of hypertensive drugs is the most effective form of therapy permitting the attainment of good results while *minimizing the adverse* effects which result from the use of large dosages of individual drugs when used singly

The side effects of various hypotensive agents should be searched for carefully thus obviating more serious consequence *of long term therapy*

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Clinical communications

Anomalous pulmonary venous drainage associated with mitral valve disease

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*Antoine Block, M.D.***
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The association of anomalous pulmonary venous drainage with mitral valve disease has rarely been reported. In the literature only 14 publications[1-14] dealing with 19 cases could be found. In 17 of these cases the anomalous pulmonary venous return was associated with stenosis of the mitral valve. In only 2 cases[13] was slight or mild mitral regurgitation noted; cases with severe mitral insufficiency were not published. (A case published by Töply[15] has been cited, but this case actually represents mitral valve disease with an anomalous superior caval vein.)

From a review of 943 cases of mitral valve disease and 70 cases of anomalous pulmonary venous return studied in our department, a combination of both conditions was found in a total of 4 cases. This might lead one to suggest that this syndrome is less rare than would be expected from the literature. In 2 of our cases a mitral stenosis was found, and in the other 2 cases severe mitral insufficiency as well was found.

It is the purpose of this paper to describe the diagnostic features that led up to the recognition of this syndrome, discussing the hemodynamic consequences with particular respect to the so-called safety valve mechanism of the anomalous pulmonary venous connection.

Case reports

Case 1. A 34-year-old fireman was admitted to the hospital in June, 1964. He complained of slight dyspnea on exertion of several years duration. For the last 2 years he noticed that the dyspneic symptoms had got worse with the onset of some episodes of vertigo, palpitations, and hemoptyses. He had no history of rheumatic fever.

The physical examination showed no signs of congestive heart failure. Auscultation revealed a loud first mitral sound, a mitral opening snap, and an apical diastolic rumble with presystolic accentuation. The second sound was split normally, the pulmonary component being accentuated. Along the left sternal border a faint systolic murmur was detected.

The electrocardiogram and vectorcardiogram showed a pattern of marked right ventricular and left atrial hypertrophy.

The chest roentgenogram (Fig. 1) showed a slightly enlarged cardiac silhouette with a prominent main pulmonary artery and an increased central pulmonary vasculature, confined mainly to the right side.

On right heart catheterization (Table I) anomalous pulmonary veins of the right middle and right upper lobes were entered from the superior caval vein. The pulmonary capillary pressure in the right upper lobe equalled the right atrial pressure, whereas the wedge pressure in the right lower lobe

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Table I Catheterization data

Location	Case 1		Case 2 (Nov 1956)		Case 2 (Dec. 1959)		Case 3		Case 4	
	Pressures (mm Hg)	O_2 sat. (%)	Pressures (mm Hg)	O_2 sat (%)	Pressures (mm Hg)	O sat. (%)	Pressures (mm. Hg)	O sat (%)	Pressure (mm. Hg)	O_2 sat. (%)
Pulmonary capillary										
Right upper lobe	(6)		(5)				(9)			
Right middle lobe	(7)		(12)							
Right lower lobe	(20)				(8)		(24)		53/20(37)	
Left lung					(8)					
Pulmonary artery	67/22(42)	79.3	36/10(18)	67.5	33/6(15)	81.2	45/18(30)	78.1	87/28(51)	71.2
Right ventricle	67/6	79.1	38/3	65.3	33/0	82.0	50/5	78.5	91/4	
Right atrium	(5)	80.5	(4)	66.7	(0)	81.4	(10)		(6)	
Superior caval vein (low)						82.5		81.0		
Superior caval vein (high)				61.0				69.6		
Innominate vein		67.0				73.8				
Inferior caval vein		68.2		83.8		78.0		74.6		
Anomalous pulmonary vein		94.1				100		98.0	72	72.9
Brachial artery		95.8		96.2						
Aorta							150/90	98.8	120/74	96.0
Left ventricle							150/6		118/2	
O_2 capacity (vol. %)	19.7		18.1		17.6		19.2		18.4	
O_2 consumption (ml./min.)	250		210		230		190		260	
Pulmonary flow (L./min.)	7.6				7.0		4.8			
Systemic flow (L./min.)	4.5				5.5		3.7			
Left-to-right shunt (L./min.)	3.1				1.5		1.1			
Vascular resistence, normally draining lung tissue (dynes sec. cm.$^{-5}$)	392				102		129			
Vascular resistence, anomalously draining lung tissue (dynes sec. cm.$^{-5}$)	950				800		1456			
Mitral valve area (cm.^{2})	1.2				2.2					



Fig. 1 Case 1 Chest roentgenogram. Increased pulmonary vasculature mainly confined to right side.



Fig. 2 Case 2 Pulmonary angiogram Left atrial and left ventricular filling diastolic phase The mitral valve appear to be severely stenotic

as elevated. A left-to-right shunt was demonstrated by oxymetry O the basis of the catheterization data, diagnosis was made of mitral stenosis associated with anomalous drainage of the right upper and middle lobes.

The patient refused surgical intervention and his condition is reported to be essentially unchanged at the present time.

Case 2 A 43-year-old laborer with clinical picture of mitral stenosis was admitted in November 1956. He had no history of rheumatic fever The catheterization data (Table I) indicated mitral stenosis of such mild degree that it did not warrant surgical intervention t this time. I November 1959 he was readmitted, complaining of marked increase in the dyspneic symptoms and syncopal attacks.

The physical examination showed no signs of congestive heart failure The cardiac rhythm was irregular = 86 per minute. The first mitral sound as moderately accentuated and t the apex mitral opening snap and a diastolic rumble were heard There as no systolic murmur and the second sound as split normally

The electrocardiogram demonstrated atrial fibrillation, but apart from that it was within the normal limits.

The chest roentgenogram showed typical mitral configuration of the heart and moderately increased pulmonary vasculature on both sides.

I December 1959 second right-heart catheterization as performed (Table I). On this occasion an anomalous pulmonary vein of the right upper lobe as entered from the superior caval vein Oxymetry demonstrated left-to-right shunt t this level. A diagnosis was made of mild mitral stenosis associated with anomalous pulmonary venous return.

Subsequently the patient sustained arterial embolism in one lower extremity for which an embolectomy was performed.

I January 1960, third right-heart catheterization was performed which yielded practically identical results as the previous one of December 1959

A pulmonary angiogram (Fig 2) suggested tight mitral stenosis contradicting the catheterization data. It was noted that only ery faint reopacification of the pulmonary artery could be seen, indicating small shunt ol me

At operation in March, 1960, large anomalous pulmonary ein draining portion of the right upper lobe and entering the superior caval vein was noted The other pulmonary eins drained normally The mitral valve orifice t the time of surgery as estimated t be less tha 0.8 cm. A closed commissurotomy and resection of the anomalously draining lung segment were performed.

The postoperative course was complicated by the development of hemorrhagic infarction of the right upper lobe. I suicide attempt in April, 1960 the patient sustained a chest trauma resulting in hematoma which ruptured i to bronchus and the pleural cavity causing empyema. A lobectomy was performed but this could not prevent the onset of septicemia with highly resistent staphylococci, as result of hich the patient died in August, 1960

On autopsy well-opened mitral al was found. It could not be determined ith certainty whether the mitral stenosis had been of rheumatic or of congenital origin.

COMMENT I this case of mitral stenosis associated with partial anomalous enous return of the right upper lobe, striking discrepancy between the calculated mitral valve orifice and the findings t operation was noted. A careful review of the catheterization data of December 1959 and January 1960 offered no definite solution t the problem As the calculation of the shunt olume ma be considered t be most liable to error it could be expected that in reality the shunt olume as larger and consequently the systemic flow lower tha was

calculated, which would result in a narrower mitral valve. However the angiogram and thorax roentgenogram both corroborated the calculation of a low shunt volume.

The only reasonable explanation seems to be, therefore, that the systemic flow as well as the pulmonary flow were lower than had been calculated, which could have been due to incorrect measurement of the oxygen consumption (The oxygen consumption was accurately measured in December 1959 but merely estimated in January 1960).

Case 3 In September 1965 a 33-year-old housewife was admitted with a history of rheumatic fever in 1944 For the last 5 years she had progressive symptoms of dyspnea and easy fatigability

On physical examination a moderately elevated jugular venous pressure was found, the liver was not enlarged, and there was no edema. Auscultation revealed an apical holosystolic murmur Grade 3/6 and third heart sound with a middiastolic murmur The splitting of the second sound was wide and fixed, with accentuation of the pulmonary component. A Grade 1/6 pulmonary systolic murmur was also noted

The chest roentgenogram demonstrated left-sided cardiac enlargement and marked dilatation of the left atrium The central pulmonary vasculature was increased

The electrocardiogram and vectorcardiogram showed pattern of right ventricular hypertrophy left atrial hypertrophy and left ventricular strain

At cardiac catheterization (Table I) an anomalous pulmonary vein of the right upper lobe was entered from the superior caval vein A left-to-right shunt was demonstrated by hydrogen curves and oximetry The pulmonary capillary pressure was markedly elevated the right lower lobe and equalled the right atrial pressure in the right upper lobe.

A left ventricular angiogram revealed severe mitral regurgitation A preoperative diagnosis was made of severe mitral stenosis and insufficiency with abnormal venous return of the right upper lobe.

At operation in May 1966 fibrosed mitral valve was replaced with Starr Edwards prosthesis. A large pulmonary vein which extended from the right upper lobe and drained into the superior caval vein was detected. Attempts to anastomose this vein to the left atrium were unsuccessful The artery to the apical segment was ligated, after which the shunt was practically completely abolished. (This was demonstrated by oxygen samples taken on the operation table.)

The postoperative course was characterized by abnormal bleeding and renal shutdown. As a result of this the patient died 15 days after operation.

Case 4 A 30-year-old secretary was known to have mitral valve disease since an episode of rheumatic fever in 1955. After a full term spontaneous delivery of a normal infant in November 1965 she had become markedly dyspneic. This improved significantly after diuretics and digoxin administration. At the time of her admission in January 1966, she was virtually symptom free.

On physical examination an accentuation of the first mitral sound and mitral opening snap was noted An apical diastolic rumble with presystolic accentuation and a holosystolic murmur Grade 3/6 was heard. The second pulmonic sound was loud and not split. The liver extended two fingerbreadths below the right costal margin but was not tender on palpation. The jugular venous pressure was elevated and there was no edema.



Fig. 3. Case 4. Chest roentgenogram. No evidence of abnormal vasculature of left upper lung field.

The chest roentgenogram (Fig 3) demonstrated left ventricular and left atrial enlargement. The main pulmonary artery was prominent and the central pulmonary vasculature was increased equally on both sides.

The electrocardiogram and vectorcardiogram showed pattern of biventricular and biatrial hypertrophy

At cardiac catheterization (Table I) a left-to-right shunt at the level of the left innominate vein was demonstrated by hydrogen curves. An anomalous pulmonary vein, with an oxygen saturation only slightly higher than the pulmonary artery, was entered easily from the left innominate vein. The relatively low oxygen saturation was rather surprising but was attributed to coexisting pulmonary arteriovenous shunts. Confirmation of this rare coincidence was obtained by pulmonary angiogram (Fig 4). Because of the minimal difference in oxygen saturation between the pulmonary artery and the anomalous pulmonary vein, the calculation of the shunt and subsequent calculation of pulmonary vascular resistance could not be performed with satisfactory accuracy

A left ventricular angiogram demonstrated stenotic calcified mitral valve and severe mitral regurgitation.

A diagnosis was made of severe calcific mitral stenosis and insufficiency associated with anomalous drainage and arteriovenous shunt of the left upper lung field.



Fig. 4 *A* and *B*. Case 4 Pulmonary angiogram (subtraction technique) *A*. Abnormal vasculature of left upper lung field with early drainage into left innominate vein and *B*. subsequent opacification of superior caval vein and right atrium.

In 1966 and 1967 the patient went through several periods of decompensation and supraventricular tachycardia. In November 1967 she had become severely decompensated and was admitted to the hospital here. Two weeks after admission her condition was complicated by a cerebrovascular accident and she died suddenly in November 1967. An autopsy was not performed.

Discussion

In Cases 1 and 2 partial anomalous pulmonary venous return was associated with tight mitral stenosis. In Cases 3 and 4 severe mitral insufficiency was also found. Case 4 represents the first reported case in which a combination with pulmonary arteriovenous shunts were demonstrated as well.

The material of this study has been taken from the records of patients with mitral valve disease and those with anomalous pulmonary venous return who have been admitted to our department for cardiac catheterization from January 1956 to December 1967. This material comprises 943 cases of mitral valve disease and 70 cases of anomalous pulmonary venous return. As a combination of both conditions was found in 4 cases, the association was present in 0.42 per cent of the cases of mitral valve disease and 5.7 per cent of the patients with anomalous pulmonary venous return.

It is remarkable that, although anomalous pulmonary venous return is associated in the majority of cases with atrial septal defect, in all our cases and in the cases reported in the literature the atrial septum was found intact.

Diagnostic features. Physical examination usually reveals signs of mitral valve disease only. It is true that a pulmonary systolic murmur may often be heard but this cannot be considered to be typical for a combination with anomalous pulmonary venous return. The electrocardiographical findings did not substantially contribute to the diagnosis.

Specific changes of the chest roentgenogram have been reported in only a few cases. In a case described by Warembourg and associates, the anomalous pulmonary vein could be seen on the plain chest roentgenogram. Aldridge and Wigle[8] noted in one case an increased pulmonary vasculature which was confined to the anomalously draining part, the same being discovered in Case 1 (Fig. 1) of our series. In Cases 2, 3, and 4 no characteristic changes of the chest roentgenogram were observed which is worth particular note in the case with pulmonary arterial-venous shunts (Case 4, Fig. 3). The diagnosis was established in all the cases at cardiac catheterization by the following findings: (1) a left-to-right shunt at the superior caval level

(2) pulmonary capillary pressures equalling right atrial pressure in the anomalously draining segments in combination with higher capillary pressures (equalling left atrial pressure) in the normally draining segments and (3) probing of the anomalous pulmonary vein of veins

The hydrogen electrode system proved to be a very sensitive and simple means of detecting and localizing the left-to-right shunt* which actually led to a correct diagnosis in Cases 3 and 4 The disadvantage of this method of not yielding quantitative data can be overcome by performing oxymetry or dye dilution studies[7] in positive cases. The finding of different pulmonary capillary pressures is highly suggestive of the syndrome but cannot be considered as conclusive since the same finding may occur in cases of triatrial heart or stenosis of a pulmonary vein

Hemodynamic features The anomalous pulmonary venous connection has been assumed by various sources to function as a safety valve thus allowing the pulmonary blood to drain via a low resistance by-pass into the right atrium In this respect the pathophysiology has been regarded to be essentially the same as in the Lutembacher syndrome[13] A number of arguments have been put forward to substantiate this concept. Varnauskas and associates[14] demonstrated in a case a rise of the pulmonary arterial pressure after occlusion of the pulmonary artery on the anomalously draining side at cardiac catheterization However only a small pressure increase was observed which indicates limited hemodynamic importance.

The observation of Bland and Sweet[15] in 1949 that in cases of mitral stenosis the clinical condition could be improved when a pulmonary vein was anastomosed with the azygos vein has also been regarded as proof of the safety valve mechanism[12] It may be noted that the longest follow up in the paper from which this conclusion was drawn was only one year and therefore this statement is open to criticism The large flow through the anomalously draining lung tissue could well lend to a rise of the vascular resistance and as a result of this a limitation of the shunt.

High vascular resistances of the anomalously draining lung tissue and consequently unimportant safety valve function was observed by Lendrum and Lichtman[4] and Adler and associates.[11] Calculations* revealed the same findings in Cases 1 and 3 of our series. In Case 4 no calculations could be made but in this case an extremely high pulmonary capillary pressure excluded the decompressive effect of the anomalous pulmonary venous connection

In conclusion from our own series and from a review of the literature we find that the safety valve mechanism is not a proved fact and that indeed in a large proportion of cases the high vascular resistance of the anomalously draining lung tissue prevents a significant decompressive effect.

*The platinum electrode catheters were routinely modified, which has been shown to improve the method.[18]

Summary

Four cases of mitral stenosis associated with anomalous pulmonary venous return are described In two of these cases there was severe mitral regurgitation as well. A pulmonary arteriovenous shunt was also found in one of these.

A review of the records of patients admitted for cardiac catheterization revealed that in 0 42 per cent of the cases of mitral valve disease and 5 7 per cent of the cases of anomalous pulmonary venous drainage both conditions were associated

The clinical roentgenologic, electrocardiographic and vectorcardiographic findings were predominantly characterized by the mitral valve disease

In every case the diagnosis was established at cardiac catheterization.

Hemodynamic studies were performed These indicated that the circulatory consequences of the mitral valve disease were only little influenced by the anomalous pulmonary venous return.

*Calculations of vascular resistances were made according to the formula

$$R(\text{resistance}) = \frac{P(\text{pressure})}{F(\text{flow})}$$

For the normally draining lung tissue P is represented by pulmonary arterial pressure minus the left atrial pressure and F is given by the systemic flow. For the anomalously draining lung tissue P = pulmonary arterial pressure minus the right atrial pressure, and F = shunt volume.

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The long term prognosis for patients resuscitated after cardiac arrest

A follow-up study

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Since the introduction of external cardiac massage[1] an increasing number of patients has been discharged after primarily successful cardiopulmonary resuscitation This paper reports on short and long term results of cardiopulmonary resuscitation in 161 patients altogether 95 patients with acute myocardial infarction (AMI) and 66 patients with cardiac arrest of mixed etiology The more significant and homogeneous group of this report the 95 patients with AMI have been studied especially to obtain an impression of how much might be achieved by setting up facilities in hospitals—such as Coronary Care Units—for a more vigorous and immediate treatment of the malignant arrhythmias that occur so frequently in this common disease. The results in the total series of 161 patients have been analyzed to evaluate to what extent it might be possible for longer periods, by means of external cardiac massage to maintain a blood flow through the brain sufficient enough to avoid serious cerebral damage

Materials and methods

The series comprises 161 patients treated for cardiac arrest (CA) in Medical Department B Rigshospitalet, Copenhagen, from 1962 to 1967 Forty-five of these cases of cardiac arrest occurred in the ward before the establishment of our Coronary Care Unit. In the remaining 116 cases treatment was initiated in the Coronary Care Unit in a little more than half of the cases, and in the emergency room or on the general medical floor for the rest. The treatment roughly followed the lines set up in an earlier publication[6] the only significant exception being that up to 1966 our first choice antiarrhythmic drug was antazoline, whereas since that time lidocaine has been the drug being used predominantly starting with a booster dose of 50 to 100 mg. given intravenously and continuing with an intravenous drip of 1 to 4 mg of lidocaine per minute

CA developed as a complication of AMI in 95 patients. Furthermore 28 patients showed significant signs of coronary artery

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Table I Etiology and results of cardiopulmonary resuscitation in 161 cases of cardiac arrest

Etiology of cardiac arrest	*Total no. of patients*	*Initially revived*	*Discharged after 4 to 12 weeks*
Acute myocardial infarction	95	59	25 (26%)
Coronary artery disease (without signs of acute myocardial infarction)	28	16	7 (28%)
Pulmonary embolism	8	5	1 (12%)
Miscellaneous	30	15	5 (17%)
Total	161	95	38 (23%)

*Table II Age distribution of 161 patients treated for cardiac arrest**

Age (yr.)	*No. of patients treated*	*No. of patients initially revived*	*No. of patients discharged*
< 50	29 (16)	20 (12)	11 (6)
50-70	91 (55)	55 (35)	20 (16)
> 70	41 (24)	21 (12)	7 (3)
Total	161 (95)	96 (59)	38 (25)

*Figures in parentheses indicate no. of patients with A.M.I.

disease in their clinical history, electrocardiogram (ECG) recordings, or at post-mortem studies, but in none of these 28 patients was definite proof of AMI revealed. Pulmonary embolism was the cause of CA in another 8 patients. A third group of patients is listed under the term miscellaneous in Table I, and this group first and foremost comprises patients with CA due to intoxication with antiarrhythmic drugs such as digoxin, quinidine, and propranolol, and CA due to electrolyte disturbances such as hypo- and hyperpotassemia.

The series included 109 men and 52 women. The age distribution and its relation to the outcome of the treatment is indicated in Table II.

Thirty-eight patients were discharged after a successful resuscitation and with the assistance of the population registers they were all traced. The follow-up study was performed in April through May, 1968, and at this time 23 of the 38 patients were still alive. Twenty-one of them were re-examined in our outpatient clinic and two answered a questionnaire. Fifteen patients had died after discharge and their death certificates were obtained and if autopsy had been performed the results of the post-mortem studied too.

The follow-up time for the surviving patients ranged between 7 months and 6 years, exceeding one year in all but 3 patients.

Results

Among 161 patients, 38 (24 per cent) could be discharged 4 to 12 weeks after CA. Among these 25 patients successfully resuscitated after CA following AMI, e.g., 26 per cent of the patients with AMI. With few exceptions resuscitation was started within 2 to 3 minutes after CA (for patients already admitted to the Coronary Care Unit even earlier. In 23 of the 38 patients the resuscitation procedures had led to successful outcome in less than 10 minutes. In 6 cases spontaneous heart action resulting in palpable arterial pulse and measurable blood pressure was restored after 10 to 20 minutes, whereas 9 patients had to be

Table III *Cardiopulmonary resuscitation**

Cause of cardiac arrest	*Total no of patients*	*Initially revived*	*Discharged after 4 to 12 weeks*
Ventricular fibrillation	80 (53)	58 (41)	25 (20)
Asystole or bradycardia	40 (20)	21 (12)	8 (3)
Pump failure	22 (14)	6 (4)	0 (0)
Unknown	19 (8)	10 (2)	5 (2)
Total	161 (95)	95 (59)	38 (25)

*Figures in parentheses indicate number of patients with A.M.I.

treated with external cardiac massage and artificial ventilation for 20 minutes up to 3½ hours (cf Table VI)

ECG's were recorded during CA in 142 of the 161 patients and the registered malignant arrhythmias and their correlation to the outcome of the resuscitation procedures are listed in Table III In this table 22 patients were classified as cases of primary pump failure as the ECG during the period where it was impossible to feel any arterial pulse showed more or less normal ventricular complexes appearing with a fairly normal rate It appears from Table III that 53 patients with AMI developed ventricular fibrillation and 20 (38 per cent) of them left hospital Out of 20 patients with AMI and CA due to asystole or bradycardia only 3 survived to discharge, whereas all patients with primary pump failure died in the hospital

In order to give an over-all impression of the long term results achieved in the patients who left hospital after treatment for CA a differentiation has been made between satisfactory and nonsatisfactory results at the follow-up the criteria of a satisfactory result being first a survival for at least one year and second a functional capacity of the patient during this year corresponding to functional class I or II according to the AHA standards. Three patients who had a follow up time of only 7 to 9 months were classified according to their functional status at the latest follow up The correlation between the etiology of the CA and long term result of the resuscitation appears in Table IV

As it is shown in this table altogether 25 patients with CA due to AMI were discharged Eleven died during the first year and 3 survived in poor health corresponding to functional class III or IV their functional capacity being reduced either by anginal pain or congestive heart failure. The remaining 11 i.e. 44 per cent of the patients with AMI thus achieved satisfactory results, as they were able to go back to work or enjoy fairly good lives as retired persons. In 10 of the 11 patients with satisfactory results, ECG's obtained during CA showed ventricular fibrillation no ECG was recorded during CA in the last patient. In the group of unsatisfactory results ventricular fibrillation had been recorded in 10 cases and asystole or bradycardia in 3 no ECG had been recorded in one.

As indicated in Table V altogether 13 late deaths have up to now been registered among the 25 patients with AMI Seven deaths occurred during the first year and 6 deaths between 1 and 6 years after the discharge. Seven of the 13 late deaths were probably caused by a new episode of cardiac arrest as it was stated that the subject died suddenly and unexpectedly

Considering the total series of 161 patients treated for cardiac arrest with external cardiac massage, serious cerebral damage was encountered fairly often in patients who died during their hospitalization after an initially more or less successful resuscitation and decerebration with ensuing disturbances of coughing, swallowing and respiration reflexes most probably contributed to the fatal outcome of at least some of these cases. However at the same

Table IV *Long-term results of cardiopulmonary resuscitation*

Etiology of cardiac arrest	*Attempts of resuscitation*	*Discharged patients*	*Satisfactory long-term results*
AMI	95	25	11 (12%)
Other diseases	66	13	7 (11%)
Total	161	38	18 (11%)

*The percentages of satisfactory results in the table have been calculated from the number of attempts of resuscitation which have been performed. Corresponding figures calculated from the number of patients discharged from hospital would be 44, 54, and 7 per cent, respectively considering patients with AMI, other diseases, and the total series.

Table V *Causes of late death in 13 patients with acute myocardial infarction resuscitated after cardiac arrest and discharged*

Cause of late death	*Total no. of patients*	*Time of late death after cardiac arrest (months)* *Less than or 3*	*3 to 12*	*12 or more*
Sudden death	7	1	3	3
Acute myocardial infarction	2	1	0	1
Congestive heart failure	2	1	0	1
Pulmonary edema	1	0	1	0
Mesenteric vein thrombosis	1	0	0	1
Total	13	3	4	6

Table VI *Duration of cardiac arrest and resuscitation in 38 patients discharged from hospital*

Duration of cardiac arrest	*No. of patients discharged*	*Satisfactory long-term results*	*Death less than 1 yr after cardiac arrest*
Less than 10 min	23 (13)	20 (11)	3 (0)
10 to 20 min.	6 (6)	2 (2)	1 (1)
20 min. to 3½ hr	9 (6)	4 (1)	5 (5)
Total	38 (25)	26 (14)	9 (6)

Figures in parentheses indicate number of patients with AMI in each group.

time 9 patients for whom it was necessary to give external cardiac massage for more than 20 minutes were discharged alive (Table VI) and in one of them the circulation was maintained by means of external cardiac massage for 3½ hours. In spite of this the latter patient recovered without any demonstrable intellectual reduction. His case history has been reported earlier. Significant intellectual reduction was seen in only one of the patients who left the hospital, whereas an anxiety neurosis developed in another. The former patient who showed significant signs of intellectual reduction was an 18-year-old girl in whom the CA was due to ventricular fibrillation

Table VII Results in four series of cardiac arrest in acute myocardial infarction

First author	Ref	No of patients with cardiac arrest	Primary resuscitation		Discharged from hospital	
			No	%	No	%
Thomas, M	12	39	14	36	9	23
Pentecost, B	9	62	33	53	19	30
Robinson J	10	38	17	45	8	21
This series	—	95	59	62	25	26

elicited by a pulmonary embolism She suddenly collapsed when walking in the street and according to the case history more than 15 minutes elapsed from the moment that she lost consciousness until resuscitation was initiated Now more than a year and a half has passed since she left hospital She is still improving and has been able to follow a course on Danish history and literature intended for young people at her own age with reasonable benefit.

Discussion

The results of cardiopulmonary resuscitation range widely from one series to another as the prognosis must be intimately related to the setting the underlying disease, and the cause of the CA [4,7,9-13] Considering solely patients with AMI Table VII summarizes the results of attempts of resuscitation in three earlier reported groups treated in hospitals with Coronary Care Units and our series. Twenty three to 30 per cent of the patients survived long enough to leave the hospital [9-12] Concerning the long term prognosis Johnson and associates[5] have published a series including 239 patients with CA complicating ischemic heart disease. Thirty three of 239 patients left the hospital after a successful resuscitation Ten died during the first year 13 survived more than one year whereas the follow up time was less than 1 year in the remaining 10 patients. The functional capacity of the patients after their discharge was not studied

Geddes and associates[4] have published their findings on a series of 50 patients with ischemic heart disease discharged after circulatory arrest caused by ventricular fibrillation. Thirty nine patients were still alive 1 to 29 months later whereas 11 had died, 5 deaths occurring within 3 months and 6 within 7 to 22 months. The observation time was more than one year in 15 patients Twenty three patients were re-examined with special reference to functional capacity Fourteen patients (61 per cent) belonged to functional classes I or II whereas 9 (39 per cent) were in classes III or IV These figures correspond fairly well to our experiences where a satisfactory long-term result, defined as more than one year survival in a functional status corresponding to class I II had been achieved in 11 out of the 25 patients discharged after AMI complicated with CA, e.g in 44 per cent of the patients.

In regard to psychiatric complications in patients surviving CA Druss and Kornfeld[3] have made extensive examinations in 10 patients. The result of their study was that serious emotional problems developed in most of the cases. These results contrast with the experiences obtained from our 38 patients discharged after CA, in whom definite signs of an anxiety neurosis developed in one case only and significant intellectual reduction in another

Summary

This paper reports on both short and long term results in the management of cardiac arrest (CA) in 161 patients, 95 of whom had acute myocardial infarction (AMI) Thirty-eight of the 161 patients were discharged from hospital, 25 of whom belonged to the group with AMI A 7 month to 6 year follow up study was performed and it was stated that 11 (44 per cent) of

the 25 discharged patients with AMI survived for more than 7 months in a functional state corresponding to functional class I or II whereas 14 died during the first year or survived in poor health corresponding to functional class III or IV In the thirty-eight patients who had been discharged after CA resuscitation procedures (including external cardiac massage and artificial ventilation) had to be continued for more than 20 minutes up to 3½ hours before spontaneous heart action was restored but at the follow-up only one of these patients showed definite signs of intellectual reduction whereas an anxiety neurosis had developed in another patient.

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Intraventricular trifascicular blocks
Review of the literature and classification

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Intermittent conduction in the anterior and posterior division of the left bundle branch in the same patient is certainly a rare event, as indicated by the 15 years elapsed before we could gather the four cases of right bundle branch block with intermittent left anterior and posterior hemiblock (RBBB with intermittent LAH and LPH) presented in the first part of this paper.[1] However, though differently interpreted when published, a few more typical cases and some others very closely related could be found in the literature. These cases had been generally considered as examples of block in the main right and left bundle branches. Yet, in a paper published in 1965[2] we deliberately omitted those cases from the corresponding review of the literature because at that time we already realized that they were not true examples of "bilateral bundle branch block." The difference between both types of syndromes will become more appar- from the following description.

Cases of RBBB with intermittent LAH and LPH found in the literature

The case of a 65-year-old woman with coronary heart disease and Adams-Stokes seizures published by Katz and associates is a typical example of RBBB with intermittent LAH and LPH. Her ECGs exhibited two different types of ventricular complexes: one, RBBB with LAH and ÂQRS at −75°, the other, RBBB with LPH and ÂQRS at +120°, and in addition, important A-V conduction disturbances. The most interesting combinations were the following. In their Fig. 1A, the tracing displayed RBBB with LAH, 2:1 A-V block, and a P-R interval of 0.28 sec. Their Fig. 2A and 2B reveals both types of ventricular complexes in a single tracing. Their Fig. 3A shows 3:2 A-V block, one beat of

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AH the next with LPH and a third P wave with no ventricular response. Their Fig 3B shows 4 3 A V block, one beat with LAH the next two with LPH (always with RBBB) and the fourth P wave with no ventricular response.

The case published by Strauss and Langendorf[4] is another typical example. The patient was a 58-year-old man also with coronary heart disease and Adams-Stokes seizures. His ECG s exhibited (Fig 1[4]) RBBB with LPH an ÂQRS at +120° a P R interval of 0.21 sec., and a QRS interval of 0 16 sec. and 17 days later (Fig 2[4]) RBBB with LAH an ÂQRS at −60° the same QRS width and A V conduction varying between 2 1 and 3 1

The preceding two cases faithfully depict all the features ascribed to the syndrome of RBBB with intermittent LAH and LPH [4] A third case also assembling the same features is contained in a paper by Langendorf and Pick[4] (their Fig 2) but is not listed here, for through that figure, it seems to be the same case that was reported in 1932 by Katz and associates.[3] Another case which also seems at first sight to be an example of the syndrome is the one published by Lilienfield and associates of a 24-year-old woman with acute myocarditis. She had a typical RBBB with LAH and ÂQRS at −75° (Fig 1A[7]) Two days later another ECG still showed RBBB (Fig. 1B[7]) but with an ÂQRS at +165° In subsequent tracings RBBB disappears, and the ÂQRS changes to about +60° One could have thought that their Fig 1B indicated the presence of LPH However this was not LPH but the rightward deviation of the ÂQRS which may be seen in uncomplicated RBBB as corroborated by the tracing without RBBB (for differential diagnosis between pure RBBB and RBBB with LPH see reference 5) Besides, there were no A V conduction disturbances. In short, the patient showed RBBB with LAH both transient, but LAH disappearing first.

Other cases closely related to the syndrome of RBBB with intermittent LAH and LPH

In the first place, we shall consider four cases reported by Barnes and Yater Mortensen, and Dressler[1] (two cases) The case by Mortensen exhibited two types of QRS complexes one with an ÂQRS at −60° the other with an ÂQRS at +120° (Lead II incorrectly recorded or mounted) The beats with an ÂQRS at +120° are typical of RBBB with LPH and have a normal P R interval On the other hand the beats with an ÂQRS at −60° are typical of LBBB (according to the chest leads) and have a prolonged P R interval. Our interpretation is as follows The patient had as in our four cases of permanent RBBB with intermittent LAH and LPH conduction disturbances in the right bundle branch and in the two divisions of the left but in contrast to those block was permanent in the posterior division and intermittent or unstable in the anterior division and in the right bundle branch Thus, sometimes conduction took place through the right bundle branch while blocked in the two divisions of the left eliciting a LBBB pattern at other times, through the anterior division while blocked in the posterior and n the right bundle branch so evoking a pattern of RBBB with LPH The LBBB pattern in this case can be considered as "divisional (*D*) i.e. due not to lesions in the trunk of the left bundle branch but in its two main subdivisions. The two cases by Dressler[1] can be interpreted in the same manner The first was a 76-year-old woman who had a clinical episode of coronary thrombosis. Her ECG s showed sometimes a pattern of LBBB with an ÂQRS at approximately 0° and a P R interval of 0 17 sec at other times, a pattern of RBBB with LPH and a P R interval of 0.23 sec. The second patient was a 51 year-old man with Adams-Stokes seizures, whose ECG s exhibited sometimes a pattern of RBBB with LPH ÂQRS at +120° and a P R interval of 0 21 sec., at other times, a pattern of LBBB with ÂQRS at −45° and a P R interval of 0.16 sec. Finally in the case by Barnes and Yater[1] (their case 1) the patient was a 74-year-old woman with some sort of primary myocardiopathy In one tracing the ventricular complexes suggested LBBB with an ÂQRS close to −60° and a P R interval of 0.20 sec In another ECG the ventricular complexes showed an ÂQRS at +90° with a large Q wave in leads II and III and a P R interval of 0 24 sec. Although this second

pattern is compatible with RBBB plus LPH it could also correspond to focal block in the posterior wall of the left ventricle with or without RBBB However the A V conduction disturbances favor the first possibility

In the second place we shall consider three cases reported by Winterberg [11] Grassberger [12] and Holzmann [13] In these cases conduction seemed to be unstable or intermittent as much in the right bundle branch as in the two divisions of the left thus providing perhaps the best experiment which can be imagined to demonstrate the trilaterality of the human intraventricular conduction system

Holzmann s patient[13] was a 28 year-old man with primary myocardial disease and Adams-Stokes seizures. His ECG s showed in addition to severe A V conduction disturbances, three main types of ventricular complexes. (1) The first type is RBBB with an ÂQRS hard to estimate possibly around −40° (qRS in Lead I RS in Lead II rSr in Lead III) These beats, which were the most common most likely indicate a certain degree of LAH added to the RBBB and were generally accompanied by the longest P R interval (2) The second type is typical RBBB with LPH with an ÂQRS at +120° These were the least common and were accompanied by a P R interval shorter than the preceding ones. (3) The third type is LBBB with an ÂQRS between −15 and −30° and the shortest P R interval (from 0 20 to 0 2? sec) Beats 1 seem to indicate that the impulse reached the ventricles through the posterior division of the left bundle branch beats 2 through the anterior division and beats 3 through the right bundle branch In general the impulse reached the ventricles through one of the fascicles only or so in advance over the other two that a pattern of block of the last two was elicited Thus the three basic patterns observed were each of them the *expression of block within two fascicles* either the right bundle branch plus the anterior division of the left or the right bundle branch plus the posterior division or the anterior plus the posterior division of the left bundle branch In addition there were some other beats transitional between types 1 and 2 For instance in Figs. 1 and 2[13] there were many beats showing LPH but with a much smaller voltage, mainly incomplete forms of LPH and in Fig. 2, the second beat shows a pattern without either LAH or LPH which might be considered as a pattern of pure or almost pure RBBB

Grassberger s[12] patient (some tracings from the same case have been published elsewhere by Scherf and Boyd[?]) was a 17 year-old woman with Adams-Stokes seizures. Autopsy showed a very severe and extensive myocarditis. In addition to severe A V conduction disturbances, her ECG s showed many different forms of ventricular complexes *of supraventricular origin.* In Figs. 3 to 7 the author[12] shows five different types of QRS contour which he catalogues as Types 1 to 5 The tracing of Fig. 3 (Type 1) with a heart rate of 83 beats per minute, shows incomplete RBBB with LAH, an ÂQRS at −60° a P R interval of 0.1? to 0.20 sec. and a QRS width of 0.10 sec. The tracing of Fig 4 (Type 2) with a ventricular rate of 110 per minute shows 2 1 A V block and as the preceding one incomplete RBBB but with LAH of much less degree, an ÂQRS at −30° and a marked reduction of the R wave in Lead I and of the S wave in Leads II and III The QRS width did not change from 0 10 sec. and the P R interval measured *0 18 to 0 19* sec. The tracing of Fig 5 (Type 3) with a heart rate of 8? per minute, again 1 1 A V conduction, and a P R interval of 0.20 to 0.21 sec., shows a QRS complex very *similar to* Type 1 with an ÂQRS again at −60° but with a QRS width now of 0 12 sec. therefore a typical pattern of RBBB with LAH Before going on we shall try to interpret these first three tracings. In the three, there was RBBB with LAH but both the degree of RBBB and that of LAH changed as the heart rate varied When the heart rate increased and 2 1 A V block thus resulted (beats Type 2 in Fig 4) the R R interval lengthened, determining a reduction in the degree of *the LAH and of the* RBBB too. In each of the three tracings, the impulse always reached the ventricles first through the posterior division of the left bundle branch But in Types 1 and 2 it also arrived through the right bundle branch not much later because of which RBBB was incomplete. In Type 2 it is also clear that the impulse arrived through the anterior d ?

sion not much later than through the posterior because of which LAH was also incomplete In the ECG of Fig 6 (Type 4) [11] with a heart rate of 93 beats per minute a typical pattern of RBBB with LPH appears, with an ÂQRS at +120° a P R interval of 0.20 to 0.22 sec., and a QRS width of 0.12 sec. It is obvious that the impulse now reaches the ventricles through the anterior division. In the tracing of Fig 7 (which Grassberger identifies as Type 5) Leads I and II seem to belong to one of the previous types and Lead III to another The QRS interval measures 0 10 sec and Leads I and II look like incomplete RBBB with LPH incomplete too with an ÂQRS at +90 or +100° On the other hand Lead III looks like uncomplicated incomplete RBBB with no trace of either LAH or LPH. Summarizing the ventricular complexes of Grassberger's patient showed (1) different degrees of RBBB (2) different degrees of LAH and (3) different degrees of LPH

Winterberg's[11] patient was a 31 year-old man with a myocardiopathy and Adams-Stokes seizures whose ECG's showed also A-V conduction disturbances together with different forms of QRS complexes. The author identifies five different types (A to E) Type A is RBBB with LAH with an ÂQRS at −60° a P R interval of 0 18 to 0.19 sec., and a QRS width of 0 18 sec. (Figs. 1A and 2[11]) Type B (Figs 1B and 5 and 7[11]) is LBBB with an ÂQRS between 0 and −30° a P R interval of 0 18 to 0.20 sec and a QRS width of 0 17 sec. Types C D and E were much more difficult to ascertain however Type C seems to begin as if it were LBBB and to end as if it were LAH On the other hand Type E seems to begin as being LBBB and to end as being LPH. The ÂQRS is at −15° in Type C and about +80° in Type E. Type D was impossible to classify (in the absence of chest leads) As in the preceding cases the different QRS contours could many times be observed in a single tracing combined with striking variations in A V conduction For instance Fig 3 shows 4.2 A V block with the first beat of Type A, the second of Type B and the next two P waves with no ventricular response. In short, the patient showed beats with RBBB plus LAH beats with LBBB and very atypical beats in which some of the features of either LAH or LPH seemed to be present. One has to assume that in beats Type A the impulse reached the ventricles through the posterior division and the right bundle branch that in Type B the impulse arrived through the right bundle branch and was blocked in both divisions of the left and in beats Type C and E, it would seem as if the impulse arrived first through the right bundle branch and then with a very small time difference through the posterior or anterior division of the left, respectively

In the third place, we shall consider seven cases reported by Richman and Wolff[14] (their Case 1) by Rosenbaum and Lepeschkin (their Case 2) by Unger and associates [8] (their Case 2) and very recently by Rosenbaum and associates[1] (the four cases in Figs. 17 to 20 of chap VIII) In each of these seven cases there were two types of QRS complexes one a pattern of RBBB with LAH the other a pattern of LBBB Sometimes both types occurred in the same tracing In the first type the impulse is assumed to reach the ventricles through the posterior division of the left bundle branch while blocked or considerably delayed in the anterior division and the right bundle branch the result being a pattern of RBBB with LAH In the second type the impulse is supposed to arrive through the right bundle branch giving place to a pattern of LBBB (of the divisional mechanism)

To recapitulate we have the following (1) Two cases by Katz and associates and by Strauss and Langendorf showing two types of QRS pattern one RBBB with LAH the other RBBB with LPH These two cases may be added to the four reported in the first part of this paper and all of them can be interpreted as indicating "permanent RBBB with intermittent LAH and LPH (2) Four cases (one by Barnes and Yater one by Mortensen and two by Dressler) exhibiting also two types of QRS complex one RBBB with LPH the other LBBB These were interpreted as indicating permanent LPH with intermittent RBBB and LAH (3) Seven cases (one by Richman and Wolff one by Rosenbaum and Lepeschkin one by Unger and associates and four by Rosenbaum and associates) showing again two types of QRS complex one RBBB with LAH the other

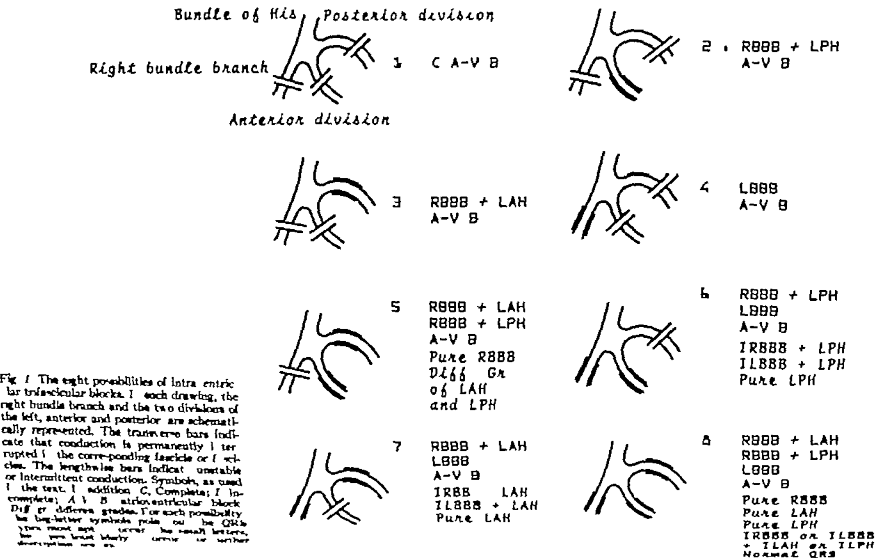


Fig 1 The eight possibilities of intra entric lar trifascicular blocks. I each drawing, the right bundle branch and the two divisions of the left, anterior and posterior are schematically represented. The transverse bars indicate that conduction is permanently I ter rupted I the corresponding fascicle or I sel-cles. The lengthwise bars indicat unstable or intermittent conduction. Symbols, as used I the text. I addition C, Complete; I Incomplete; A V B atrioventricular block Diff Gr different grades. For each possibility [illegible]

LBBB. These cases were interpreted as indicating "permanent LAH with intermittent RBBB and LPH." (4) Finally, three cases (one by Holzmann, one by Grassberger, and one by Winterberg) showing a larger and more complex variety of ventricular complexes. In Holzmann's patient, there were three main types: one RBBB with LAH, another RBBB with LPH, and the third LBBB. In addition, some transitions between LAH and LPH associated with RBBB and occasionally some beats with pure RBBB. Grassberger's patient showed the association of different degrees of RBBB, LAH, and LPH, giving place to at least four or five different QRS contours. Winterberg's patient showed two different types of ventricular complexes: one, RBBB with LAH, another LBBB, and two others, looking like incomplete LBBB associated with LAH and LPH, respectively. These last three cases were interpreted as indicating "RBBB, LAH and LPH, all intermittent."

If we now consider all these cases together, it is clear that they have in common the existence of a conduction disturbance within the three main terminal fascicles of the intraventricular conduction system, namely, the right bundle branch and the anterior and posterior division of the left. The extent to which block is permanent or intermittent in the three fascicles is what makes these cases differ from one another. Although from an anatomicoclinical point of view they can all be considered as belonging to the same family, from a pure electrocardiographic standpoint they can perhaps best be grouped in different syndromes, undoubtedly very much interrelated. We call them as a whole the "intraventricular trifascicular blocks."

The varieties of intraventricular trifascicular blocks

The syndrome of "permanent RBBB with intermittent LAH and LPH" was our first evidence of the existence of intraventricular trifascicular blocks.[4] However, the above review has shown that other syndromes do exist which, though electrocardiographically expressed in a somewhat different way, belong to the same family.

With such a groundwork, it was not very difficult to devise a theoretical design covering all the different possibilities of intraventricular trifascicular blocks. Such a design is presented in Fig. 1 and elaborated in the following text.

In Fig. 1, the different QRS contours listed beside each corresponding drawing in big letters are the ones most apt to occur and these do occur whenever the differences among the conduction times of the three fascicles are enough to elicit the pattern of "complete" block of the most affected fascicle or fascicles. However, if an impulse arrives through two fascicles (or through the three) with time differences lower than the corresponding "critical differences," the beat will show a pattern of "incomplete" block of the corresponding fascicle or fascicles. These possibilities, less likely to occur, are listed in the diagram of Fig. 1 in small letters.

1. If conduction is completely interrupted in the right bundle branch and in the two divisions of the left, complete heart block occurs (Fig. 1, possibility (*P*) 1). This has been produced experimentally in the dog and reasonably proved in human clinical cases. However, if the conduction disturbance is unstable or intermittent in one, in two, or even in the three fascicles, a series of different electrocardiographic syndromes may take place (Fig. 1, *P2* to *P8*).

2. *P2, 3, and 4* correspond to the three possible situations in which block is complete and permanent in two fascicles and intermittent in the third. In *P2* (permanent block in the right bundle branch and in the posterior division of the left, and intermittent in the anterior) the ECG will show RBBB with LPH and different forms of A-V block. In *P3* (permanent block in the right bundle branch and in the anterior division and intermittent in the posterior) the ECG will show RBBB with LAH and different forms of A-V block. In *P4* (permanent block in the two divisions of the left bundle branch and intermittent in the right) the ECG will show LBBB and different forms of A-V block. *P2* has been shown in a series of cases of RBBB with LPH reported elsewhere, where most of the cases proved to be associated with advanced degrees of heart block. *P3* has also been demonstrated in a group of cases of RBBB with LAH accompanied by A-V conduction disturbances. As for *P4*, we all

must recall having seen cases of LBBB with severe A V block And though it is perfectly true that the A V block could be due to A V node or main bundle lesions or to bilateral bundle branch block at least some of those cases could be examples of *P4*

3 *P5 6 and 7* correspond to the three possible situations in which block is complete and permanent in one of the fascicles only and intermittent in the other two In *P5* (permanent block in the right bundle branch and intermittent in both divisions of the left) the ECG will show RBBB with LAH RBBB with LPH and different forms of A V block In addition in beats in which the conduction times in both divisions of the left bundle branch were only slightly different transitions will occur showing different degrees of incomplete LAH and LPH (according to the beat) always accompanied by RBBB and in the rarer instance in which both conduction times were exactly equal (or keeping to each other the relationship which these have under normal conditions) the corresponding beats will show neither LAH nor LPH and a pattern of pure RBBB will occur *P5* has been well documented by the four cases presented in the first part of this paper and by the cases of Katz and associates[3] and Straus and Langendorf[4] already commented upon (see above) In *P6* (permanent block in the posterior division of the left bundle branch and intermittent in the anterior and in the right bundle branch) the ECG will show RBBB with LPH LBBB and different forms of A V block In addition in beats in which the conduction times within the right bundle branch and the anterior division of the left were very similar to each other two variants may occur If the impulse reaches the ventricles through the anterior division first, but only slightly in advance over the right bundle branch the corresponding beat will show a smaller degree of RBBB associated to the LPH conversely if the impulse coming through the right bundle branch is the one arriving slightly before ventricular activation will *start as if it were* a case of LBBB and will close as if it were a case of *LPH* resulting in a pattern of incomplete LBBB with LPH In the rare and fortuitous instance in which the conduction times in the right bundle branch and in the anterior division of the left keep to each other the same relationship existing under normal conditions (no matter if those conduction times are really normal or prolonged) the corresponding beat will show a pattern of *pure LPH* with no trace of RBBB present *P6* seems to be well exemplified by the observations of Barker and Yater [illegible] Mortensen [illegible] and Dressler [illegible] analyzed in the preceding section of this paper In *P7* (permanent block in the anterior division of the left bundle branch and intermittent in the posterior and in the right bundle branch) the ECG will show RBBB with LAH LBBB and different forms of A V block. In addition in beats in which the total conduction times within the right bundle branch and the posterior division of the left were very close to each other two variants may occur If the impulse arrives first through the posterior division, the degree of RBBB (associated to the LAH) will be less conversely if it arrives slightly earlier through the right bundle branch ventricular activation will *start as if it were* a case of LBBB and will *terminate as if it* were a case of LAH the end result being a pattern of incomplete LBBB with *LAH* In the rare instance in which the conduction times in the right bundle branch and in the posterior division of the left were "normally" related the beat will exhibit a pattern of pure LAH with no trace of RBBB *P7* seems to be well exemplified by the cases of Richman and Wolff,[illegible] Rosenbaum and Lepeschkin,[illegible] Unger and associates,[14] and Rosenbaum and associates[illegible] already analyzed in this paper

4 *P8* corresponds to the situation in which there is unstable or intermittent block within the three fascicles The ECG will show RBBB with *LAH* RBBB with LPH and LBBB (in every beat in which the impulse reaches the ventricles through one channel well in advance over the other two) and of course *different forms of A V* block If the impulse arrives with normal or diminished but equal speed through two fascicles and later on through the third, beats with pure LAH pure *LPH* and pure RBBB may show up In the special case in which the impulse arrives into the ventricles through the three fascicles, but with very small time differences among them quite a number of combinations will be apt to

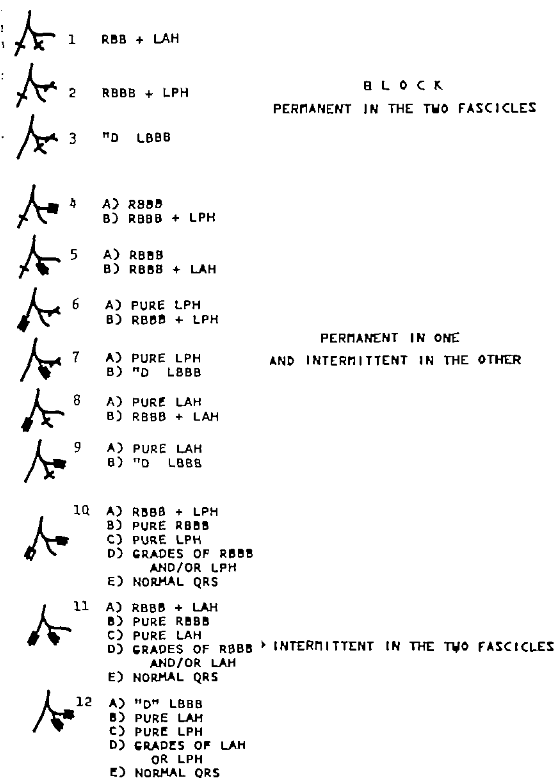


Fig. 2. The twelve possibilities of intraventricular bifascicular blocks (excluding bilateral bundle branch block). Symbols, as Fig. 1 except "D" standing for "divisional"

occur including different degrees of incomplete RBBB LAH or LPH In these combinations, not only the QRS contour but also the QRS width will vary *P8* seems to be very well exemplified by the cases of Holzmann[11] Grassberger[12] and Winterberg[13] previously described and analyzed

It must be clear by now that each one of the eight possibilities included in the theoretical design of Fig 1 actually occurs or may occur though uncommonly in clinical practice The author coming across any one of those peculiar electrocardiographic situations might be led to believe that he is facing a new electrocardiographic syndrome which according to the particular case he will be able to designate as follows (1) RBBB with LAH and LPH all permanent (this is the only situation with no specific electrocardiographic expression) (2) permanent RBBB and LPH with intermittent LAH (3) permanent RBBB and LAH with intermittent LPH (4) permanent LAH and LPH with intermittent RBBB (5) permanent RBBB with intermittent LAH and LPH (6) permanent LPH with intermittent LAH and RBBB (7) permanent LAH with intermittent LPH and RBBB (8) RBBB LAH and LPH all intermittent After this listing it is quite evident that all these syndromes must have, as a common anatomicoclinical basis a severe damage of the whole intraventricular conduction system What varies is their physiological behavior and hence their electrocardiographic expression. It must also be very clear that altogether they constitute a very powerful argument supporting the trilaterality of the human intraventricular conduction system and the existence of the *hemiblocks* of the left bundle branch system.

If the human intraventricular conduction system can operate as trifascicular it is obvious that different possibilities of bifascicular blocks may also occur—disregarding the so-called bilateral bundle branch block.[2] These possibilities are listed in the diagram of Fig 2 Though greater in number these are much easier to understand and the diagram is thus self-explanatory It must be pointed out however that the cases showing different QRS contours in one single tracing are much less common in bifascicular blocks This is possibly related to the fact that there are no AV conduction disturbances (at least as a constant feature) in bifascicular blocks as contrasted to trifascicular blocks for as long as any one of the three fascicles functions normally AV conduction will be normal, provided there are no disturbances in AV nodal or main bundle conduction. The existence of AV block, particularly second degree, with its varying diastolic intervals promotes more favorable conditions for changes in the speed of conduction within fascicles where impulse transmission is impaired but not wholly interrupted

Summary

The right bundle branch and the two divisions—anterior and posterior—of the left constitute the three main terminal fascicles of the intraventricular conduction system. Depending on whether conduction is permanently or only intermittently interrupted in these three fascicles, eight different possibilities or combinations of intraventricular and atrioventricular conduction disturbances may occur A theoretical design covering all those possibilities is suggested and clinical examples are featured for each of them. The existence of these syndromes which we have termed altogether trifascicular blocks provides one of the most valuable evidences of the anatomical and functional "trilaterality" of the human intraventricular conduction system

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The natural history of atrioventricular conduction defects in acute myocardial infarction

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Complete heart block occurs in 5 to 7 per cent of patients with acute myocardial infarction and is associated with an increased mortality rate.[1-4] The development of coronary care units has made it possible to study the development of complications of acute myocardial infarction but there is little information available concerning the natural history of atrioventricular (A V) conduction disturbances and the development of complete heart block We here report an analysis of our experiences with A V conduction disturbances in acute myocardial infarction with particular reference to their development and progression.

Patients and methods

The 446 patients with definite acute myocardial infarction who were admitted to the Coronary Care Unit at the Royal Melbourne Hospital between May 1963 and July 1968 form the basis of this report. The clinical state of the patients on admission was assessed as mild severe or cardiogenic shock as previously defined[5] The time of onset of infarction was taken as the onset of severe or persistent pain All patients were monitored continuously and a 10 second strip of a single lead electrocardiographic recording was taken each hour or more frequently if abnormalities were noted These recordings and the daily standard 12-lead electrocardiograms were examined for evidence of altered A V conduction.

First degree heart block was diagnosed if the P R interval exceeded 0.20 sec in the majority of complexes in a tracing. Second degree heart block was diagnosed when there was intermittent failure of A V conduction Complete heart block, however transient, was classified as such. Transient heart block following direct current countershock was not included A V conduction defects occurring in the last few minutes of life in patients with cardiogenic shock were regarded as terminal and were also excluded

All patients were treated with oral anticoagulants unless contraindicated Heart failure was treated with digitalis and diuretics, and lidocaine procainamide propranolol and diphenylhydantoin were the antiarrhythmic drugs used.

The management of A V conduction

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Table I Site of infarction related to degree of A-V conduction defect and mortality rate

No. of patients	Anterior		Inferior		Anterior and inferior		Undetermined site		Total	
	No.	Mortality rate (%)	No.	Mortality rate (%)	No.	Mortality rate (%)	No.	Mortality rate (%)	No.	Mortality rate (%)
Total	239 (52%)		190 (42%)		13 (3%)		14 (3%)		446 (100%)	
No. with first, second, or third degree A-V block	9 (4%)	56	35 (18%)	17	7 (54%)	100	3 (21%)	0	54 (11.5%)	33
No. with third degree block	5 (2%)	80	16 (8%)	25	5 (38%)	100	3 (14%)	0	29 (6.5%)	45

Table II The relationship between degree of heart block, clinical severity, and outcome

Maximum degree of heart block	Mild		Severe		Shock		Total		% of total C.C.U. group
	No.	Mortality rate (%)	No.	Mortality rate (%)	No.	Mortality rate (%)	No.	Mortality rate (%)	
First	5	0	5	20	0		10	10	2
Second	6	0	8	50	1	0	15	27	3
Third	3	33	21	33	5	100	29	45	6.5
Total	14	7	34	35	6	84	54	33	11.5

disturbances varied over the period under review. Four of the 21 patients with second degree block and 14 of the 29 with complete heart block were paced, while the others were treated with drugs.

Results

The overall hospital mortality rate of the 446 patients was 25 per cent. Fifty-four (11.5 per cent) of the 446 patients developed some A-V conduction defect; this group had a hospital mortality rate of 33 per cent. The 29 patients who developed complete heart block had a mortality rate of 45 per cent.

The site of infarction determined from the electrocardiogram or autopsy related to the degree of A-V conduction defect and the mortality rate is shown in Table I.

The 13 patients with evidence of anterior and inferior infarction were those admitted to the Unit with a second acute infarction in the presence of electrocardiographic evidence of the previous infarction. A high proportion (54 per cent) of the patients in this group developed conduction defects with an associated mortality rate of 100 per cent. In 14 patients, although there was clinical and enzyme evidence of infarction, the site could not be designated anterior or inferior. The group included patients with subendocardial infarction and left bundle branch block.

Of the 29 patients with complete heart block, 16 had inferior infarction (mortality rate 25 per cent) and 5 patients had anterior infarction (mortality rate 80 per cent). Three of the 5 with recent anterior

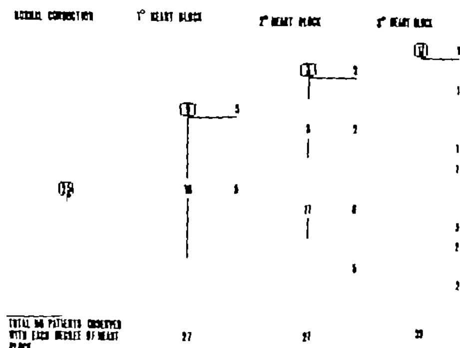


Fig *1* Progression of A V conduction disturbances in the 54 patients. The figures in squares represent the number of patients admitted in that particular state of conduction. Recorded progression to more advanced degrees of heart block is indicated by lines and figures in the appropriate columns.

infarction had electrocardiographic evidence of bilateral bundle branch block.[3] The 5 patients with anterior and inferior infarction and complete block all died but in each case after return to sinus rhythm Three patients in the site undetermined group were admitted with left bundle branch block and third degree A V block These 3 were admitted to the Unit 3 5 and 7 days after the acute infarction They survived and were the only patients requiring permanent cardiac pacing The other patients in the group had clinically mild infarction associated with first and second degree block and no hospital mortality

Table II relates the degree of heart block the clinical severity and the outcome. With the more severe degrees of heart block there was an increasing mortality rate from 10 per cent with first degree heart block to 27 per cent with second degree heart block and to 45 per cent with complete heart block. More severe degrees of heart block were associated with more serious infarction as assessed clinically on admission. Seventeen of the 29 patients with complete heart block were admitted with this conduction disturbance and so it was not possible to assess how much the heart block contributed to the worsened clinical state

Fig 1 illustrates the recorded changes in A V conduction in the patients during the period of observation. Thus, [illegible] and 17 were admitted to the Coronary Care Unit in sinus rhythm first degree second degree and complete heart block respectively

Of the 21 patients in whom second degree heart block was recorded, seven [illegible] per cent) progressed to complete heart block This figure may be low since [illegible] the patients were paced with fixed [illegible] pacemakers which may have [illegible] the development of complete heart block. Of these 21 patients with second degree heart block 17 had inferior infarction alone while the other 4 had combined anterior and inferior infarction. There were none with anterior infarction alone. The [illegible] of the 4 patients with combined anterior and inferior infarction progressed to complete heart block but none [illegible]

Table III *Outcome of 27 patients with first A V block**

Outcome	Anterior	Inferior	Anterior and inferior	Total	Mortality rate (%)
Remained in first degree block	3	7 (1)	—	10 (1)	10
Progressed to second degree block	—	7	1 (1)	8 (1)	12
Progressed to third degree block	2 (2)	6 (2)	1 (1)	9 (5)	56
Total	5	20	2	27 (7)	26

*Figures in brackets represent the number of deaths within the group.

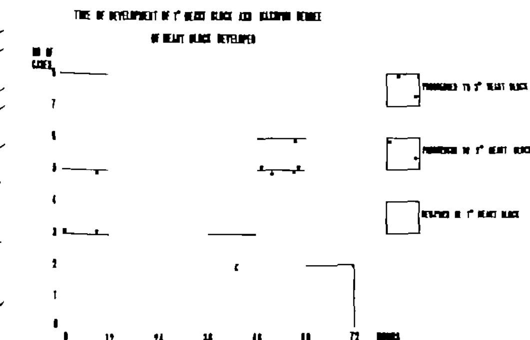


Fig. 2. A diagram illustrating the time of development of first degree heart block in relationship to the maximum degree of heart block developed in each patient.

severely on developing complete heart block. In 20 of these 21 patients, the Wenckebach phenomenon was recorded at some time.

In the 27 patients in whom first degree heart block was recorded 10 did not progress to more advanced heart block, 8 progressed to second degree heart block, while the other 9 ultimately progressed to complete heart block (Table III). The mortality rate of the group of patients with first degree heart block (10 per cent) was not altered by progression to second degree heart block (mortality rate 12 per cent) but the development of complete heart block in this group was associated with an increase in mortality rate to 56 per cent. In this small group some patients with infarcts at each site progressed to more advanced heart block. There was no clear relationship between the anatomical site of the infarction and the likelihood of progression from first degree heart block to complete heart block.

In the 12 patients who developed complete heart block under observation in the Coronary Care Unit it was noted that the 3 with anterior infarction developed com-

Table IV Time of onset and outcome of most advanced form of heart block

Degree	No. of patients/ no. of deaths	1 to 24 h (1st 24 hr)	25 to 48 h (2nd 24 hr)	49 to 72 hr (3rd 24 hr)	>72 hours	Total
First degree	No	5	3	—	2	10
	Death (mortality rate)	0 (0%)	1 (33%)	—	0 (0%)	1 (10%)
Second degree	No	5	5	4	1	15
	Deaths (mortality rate)	1 (20%)	2 (40%)	1 (25%)	0 (0%)	4 (27%)
Third degree	No.	15	6	8	—	29
	Death (mortality rate)	9 (60%)	3 (50%)	1 (12.5%)	—	13 (45%)

plete heart block suddenly without preceding second degree A V block and they died soon afterward By contrast, 7 of the 8 patients with inferior infarction had preceding second degree heart block.

Fig 2 relates the times of onset of first degree heart block in the 27 patients with first degree heart block with the numbers progressing to more severe degrees of block It can be seen that approximately 50 per cent of each group of patients in the first four 12 hour periods developed complete heart block. After 48 hours, the proportion who developed complete heart block was only 17 per cent though a large number did develop second degree heart block In the first 48 hours there was no clear relationship between the times of onset of first degree heart block and the likelihood of developing complete heart block.

Table IV compares the times of onset of the most advanced degree of heart block in each patient with the mortality rate The 8 patients who developed complete heart block after 48 hours had a lower mortality rate (12 5 per cent) than the 21 patients in whom it occurred earlier (57 per cent) Six of these had inferior infarction one had left bundle branch block and the others had combined anterior and inferior infarction

Of the 417 patients admitted to the Coronary Care Unit with normal A V conduction only 9 (2 per cent) ultimately developed complete heart block

Discussion

The incidence (6.5 per cent) and mortality rate (45 per cent) for patients with complete heart block in the Coronary Care Unit at the Royal Melbourne Hospital was similar to that of other groups.[1-4,11] Of the 29 patients with complete heart block 16 (55 per cent) had inferior infarction and 5 (17 per cent) had anterior infarction—a threefold difference The mortality rate of patients with anterior infarction with complete heart block (80 per cent) was three times that of patients with inferior infarction thus complicated (25 per cent) The mortality rate for inferior infarction complicated by complete heart block is the same as the mean of the entire series. These differences between anterior and inferior infarction can be attributed to the difference in pathogenesis of heart block at the two sites.[3,4,13,17] This also accounts for important differences in the natural history of A V conduction disturbances. In anterior infarction, complete heart block develops suddenly usually without second degree heart block and the ventricles are activated by a focus low in the bundles or even in ventricular muscle. The ventricular rate is slow the QRS complex is widened and ventricular standstill and ventricular fibrillation are commonly seen. By contrast complete heart block complicating inferior infarction usually develops slowly and second degree heart block with the Wenckebach phenomenon is the rule. The ventricles are excited from a low nodal focus and have a rate of about 50 beats per minute. The QRS complex may not be widened. Clinical deterioration of the patient and dangerous arrhythmias are not common. Our experiences as described are in keeping with these differences.

All of the 7 who developed conduction disturbances complicating a second infarction died. A similar experience is reported by Saltups and associates.[14] The poor prognosis cannot be attributed to the conduction disturbance alone, since normal conduction had returned before our patients died. Nor can it be attributed to recurrent myocardial infarction alone, since the mortality rate of such a group is in the order of 37 per cent.[15] It is likely that the A-V conduction disturbance in this group reflects extensive myocardial damage following the occlusion of two major vessels and this would account for the high mortality rate.

As a group, the patients who developed complete heart block with acute myocardial infarction had suffered a more severe infarction and had a higher mortality rate[1-11] (Table II). Since clinically more severe infarction is associated with a greater mortality rate even without heart block[6] and that of patients with inferior infarction is no more than that of the whole Coronary Care Unit group, it can be inferred that complete heart block may complicate inferior infarction of average severity. It can also be inferred that complete heart block must complicate the severe or extensive anterior infarction and the severity of this infarction itself will contribute to the poor prognosis of this group.

The development of reliable demand-type pacemakers now makes it advisable to pace all patients with complete heart block in order to provide a means of controlling rate and allowing greater freedom in the use of digitalis and antiarrhythmic drugs. Although the insertion of a pacing catheter before the development of complete heart block or ventricular standstill has all the advantages of an elective rather than an emergency procedure, our review suggests this to be useful in limited circumstances. Theoretically, the insertion of a pacing catheter prior to the development of complete heart block would be of greatest value in those patients where complete heart block developed suddenly with severe hemodynamic deterioration or death. This is the case with complete heart block complicating anterior myocardial infarction. By contrast, the insertion of a pacing catheter prior to the development of complete heart block would be of no value when this is not associated with deterioration or death, which is the case in inferior infarction. For this reason, we do not feel that second degree heart block is an indication for endocardial pacing, since it was not seen complicating anterior myocardial infarction and it was not in itself a dangerous state in patients with inferior infarction or combined anterior and inferior infarction. In addition to this, progression to complete heart block occurred in only 33 per cent of cases in our experience and in 44 per cent of 18 cases reported by Lown.[13]

It is stated that first degree heart block is not an indication for endocardial pacing. However, in the special case of anterior infarction and first degree heart block, 2 of our patients developed complete heart block suddenly and died. It is possible that these patients may have benefited from endocardial pacing. Although the numbers are small, we feel endocardial pacing in these patients may be rewarding because of this high risk of death following development of complete heart block. First degree heart block in inferior or combined anterior and inferior infarction is not an indication for pacing for the same reasons as indicated above with second degree heart block.

Since heart block complicating anterior infarction is due to interference with conduction in both right and left bundles,[3, 18] the presence of bundle branch block may indicate a patient at risk. In reviewing 415 of the 446 patients in this series, we concluded that bundle branch block was not an indication for pacing. However, frequent standard electrocardiograms should be performed in these patients in an attempt to detect the features of bilateral bundle branch block, which is an indication for pacing.

It has been suggested[11] that the development of complete heart block within the first 24 hours carries a particularly unfavorable prognosis, but we have found that the development of complete heart block in either the first or second 24 hours carries a similarly poor prognosis. The prognosis is better if complete heart block develops after 48 hours. This is probably related to a larger proportion of inferior infarctions in the group.

Unfortunately, the time of onset of first

degree heart block and the site of infarction was of no value in predicting those who were to progress from first degree heart block to complete heart block

Summary

Of 446 patients admitted to the Coronary Care Unit 54 (11 3 per cent) developed A V conduction disturbance with a mortality rate of 33 per cent. Twenty nine had complete heart block with a mortality rate of 45 per cent There were three times as many patients with inferior infarction than anterior infarction and their mortality rate was only one third that of the latter Approximately one third of those patients who developed first degree heart block progressed to complete heart block and about one third of those who developed second degree heart block developed complete heart block In those with first degree heart block the site of infarction and time of onset was of no value in predicting those patients who might progress to complete heart block It is suggested that the prophylactic insertion of an endocardial pacing catheter prior to the development of complete heart block is of little value in patients with inferior infarcts but may be of value in those with anterior infarcts who develop first degree block

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Diagnostic value of the first heart sound in children with atrial septal defect

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It is well known that the second heart sound plays a significant role in the diagnosis of uncomplicated atrial septal defect of the ostium secundum type (ASD) -4 however there are only a few reported studies of the first heart sound in this regard In 24 children with atrial septal defect we have found abnormal phonocardiographic changes in the first heart sound which disappeared soon after surgery To the best of our knowledge similar changes in a large series of children have not been reported previously It is the purpose of this study to analyze the phonocardiographic changes observed in the first heart sound before and after surgery

Materials and methods

The present study is based on the pre and postoperative phonocardiograms of 24 children with ASD who underwent cardiac surgery during the preceding 6 years (1962 through 1968) Their ages ranged from 4 to 16 years. Seven were males and 17 were females Cardiac catheterization and angiocardiography were performed in all patients before surgery (Table I) The diagnosis of ASD was confirmed in all of them at the time of surgery In each case the defect was closed under direct vision with the use of extracorporeal circulation.

Phonocardiograms prior to 1967 were taken by means of a 4 channel photographic recording system (Sanborn Model 564 Poly Beam) at 75 mm. per second and frequencies of 400 200 100 and 50 cycles per second. For the past 2 years different recording equipment was utilized (Schwarzer Model ST 68650) Tracings were obtained at 100 mm. per second in the following frequency ranges 250 to 600 140 to 250 70 to 140 and 30 to 70 cycles per second. They were recorded over the apex, the fifth left intercostal space near the sternum the third left intercostal space near the sternum and the second left and second right intercostal spaces near the sternum Recordings were obtained during normal respiration and short periods of apnea while the patient was in the supine position. The phases of respiration were regis-

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Table 1 Summary of clinical and hemodynamic features

Patient No	Age (yr)	Sex	Clinical findings: Frequent respiratory infection	Decreased exercise tolerance	Congestive heart failure	Hemodynamic findings: Qp/Qs ratio	PVR/SVR ratio	PRI (units)	PAP (mm Hg)	
1	6	M	+	0	0	2/1	1/6	1 2	25/6	[illegible]
2	4	F	+	+	+	3 6/1	1/30	0 6	48/16	[illegible]
3	8	F	0	0	0	2 2/1	1/25	0 9	30/14	[illegible]
4	8	M	+	+	0	1 8/1	1/12	0 9	27/8 m	[illegible]
5	9	M	0	+	0	3/1	1/11	2 1	23/5 m	[illegible]
6	7	F	0	0	0	1 8/1	1/10	0 6	30/15	
7	7	F	0	0	0	1 9/1	1/21	0 9	31/7	[illegible]
8	16	F	0	0	0	2 9/1	1/20	0 9	30/12	[illegible]
9	13	F	0	0	0	5/1	1/16	0 1	15/7	[illegible]
10	4	M	+	+	+	2 9/1	1/21	0 9	28/9 m	[illegible]
11	4	F	+	+	+	5/1	1/5	3 0	33/10 m	
12	6	F	+	0	0	1/1	1/10	1 0	30/10	[illegible]
13	7	F	+	0	0	1 6/1	1/7	2 3	32/12 m	
14	1	F	+	0	0	1/1	1/9	2 0	29/14 m	[illegible]
15	4½	M	+	0	0	2 1/1	1/14	1 1	25/10 m	[illegible]
16	5	M	+	0	0	1 6/1	1/13	1 3	25/10 m	[illegible]
17	8	F	+	0	0	1 4/1	1/5	0 9	22/6 m	[illegible]
18	13	F	+	+	0	4 5/1	1/9	1 0	22/4 m	[illegible]
19	15	F	+	0	0	2 1/1	1/16	1 3	27/8 m	[illegible]
20	17	F	+	0	0	2 5/1	1/12	2 2	34/14 m	[illegible]
21	4	F	+	0	0	1 3/1	1/6	2 2	42/15 m	[illegible]
22	7	F	+	0	0	1/1	1/8	2 1	30/11	[illegible]
23	4½	F	+	+	+	2 1/1	1/15	0 8	27/9 m	[illegible]
24	4½	M	+	0	0	2 4/1	1/10	1 6	27/15 m	[illegible]

Abbreviations Qp Qs Pulmonary flow index (L min M²) systemic flow index (L min M²) PVR, SVR, pulmonary arteriolar vascular resistance (units) systemic arteriolar vascular resistance (units) PRI pulmonary arteriolar vascular resistance
PAP pulmonary arterial pressure
Diagnosis of atrial septal defect as established by cineangiocardiogram

tered by a marker manipulated by an observer who watched the movements of the chest Postoperative phonocardiograms were taken in some patients as little as 1 week and in others as long as 5 years after surgery (Fig 1) Lead II of the electrocardiogram was taken simultaneously with the phonocardiogram for reference. Indirect carotidograms were obtained in the majority of the patients but not in all

Measurement of the time interval was made in each phonocardiographic tracing from the beginning of the Q wave to the mitral and tricuspid components of the first heart sound The tricuspid component of the first heart sound was identified for the purpose of this study as the second component of a split first heart sound occurring 0 05 to 0 10 sec after the beginning of the Q wave. The pulmonary and aortic areas were carefully studied to rule out the presence of ejection clicks, notably in 2 patients in whom the tricuspid component of the first heart sound was recorded 0 12 sec after the beginning of the Q wave.

The splitting of the first heart sound ($M_1 T_1$) was corrected for heart rate in accordance with the formula $\frac{M_1 T_1}{\sqrt{RR}}$

This was done in order to compare the pre and postoperative measurements. Each value obtained was the mean result from at least 3 determinations on each patient. The T_1 M ratio was determined in each case and critically analyzed. The T M ratio was correlated with the size of the

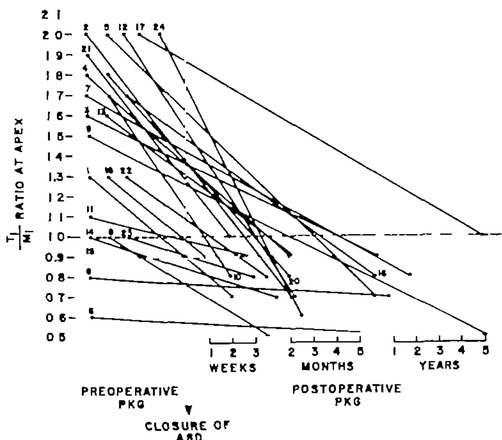


Fig. 1 Distribution and changes in T_1/M ratio of the first heart sound at the apex in phonocardiograms taken before and after closure of atrial septal defect (Patients 1 to 24).

left to right shunt, with the pulmonary artery pressure, and with the presence of right ventricular hypertrophy as manifested by the height of the R wave in Lead V_1 of the electrocardiogram.

Clinical and hemodynamic findings. Table I summarizes the most significant clinical and hemodynamic findings of this series before surgery. Frequent respiratory infections were present in all but 6 patients (Patients 3, 5, 6, 7, 8, and 9). Decreased exercise tolerance was present in 7 patients (Patients 2, 4, 5, 10, 11, 18, and 23). Heart failure was treated with digitalis before surgery in 4 patients (Patients 2, 10, 11, and 23), while 5 patients (Patients 3, 6, 7, 8, and 9) were asymptomatic.

Oxygen saturation studies performed during cardiac catheterization revealed the presence of a left to right shunt at the atrial level in all patients except 3 (Patients 12, 14, and 22). In these patients, the diagnosis of ASD was established by cineangiocardiography. With the exception of 3 patients (Patients 2, 11, and 21) in whom mild pulmonary hypertension was found, the rest of the group had normal pulmonary artery pressures. The pulmonary vascular resistance was normal in all patients. The pulmonary and systemic flow index (liters per minute per square meter) was calculated by the Fick principle. The ratio of the two indexes Qp/Qs ranged from 1/1 to 5/1 in the patients studied.

Electrocardiographic findings. Table II summarizes the electrocardiographic findings before surgery in the patients studied. Regular sinus rhythm was present in all patients. Abnormal P waves indicative of right atrial enlargement were found in 5 patients (Patients 1, ... 10, 11, and 23). The P-R interval corrected for heart rate was prolonged in 3 patients (Patients

Table II *Summary of electrocardiographic findings*

Patient No	Rhythm (RSR*)	P-wave amplitude (mm.)	$\frac{PR}{\sqrt{RR}}$ (sec.)	QRS duration (sec.)	ÂQRS axis in frontal plane (degrees)	rSR' in V	R' wave amplitude (mm.)	Right atrial enlargement	Right ventricular hypertrophy
1	+	3 0	0 19	0 07	+110	+	11	+	+
2	+	3 0	0 18	0 06	+110	+	14	+	+
3	+	0 5	0 16	0 06	+ 95	+	5	0	0
4	+	1 0	0 19	0 08	+135	+	5	0	0
5	+	1 0	0 23	0 09	+110	+	5	0	0
6	+	1 5	0 20	0 07	+150	+	10	0	+
7	+	2 0	0 18	0 06	+ 60	+	2	0	0
8	+	1 0	0 18	0 09	+ 20	+	20	0	+
9	+	2 0	0 19	0 06	+ 90	+	7	0	0
10	+	3 0	0 20	0 12	+120	+	25	+	+
11	+	2 5	0 19	0 05	+135	0	4	+	+†
12	+	1 5	0 22	0 06	+ 70	+	6	0	0
13	+	0 5	0 14	0 05	+100	+	6	0	0
14	+	1 0	0 22	0 06	+ 15	+	4	0	0
15	+	1 5	0 16	0 08	+ 75	+	8	0	0
16	+	1 0	0 16	0 05	+ 15	+	8	0	0
17	+	1 5	0 18	0 08	+ 90	+	10	0	0
18	+	2 0	0 18	0 07	+ 90	+	20	0	+
19	+	1 5	0 20	0 08	+100	+	8	0	0
20	+	1 0	0 20	0 07	+ 60	+	12	0	0
21	+	0 5	0 15	0 05	+120	+	5	0	0
22	+	1 0	0 15	0 07	+ 90	+	11	0	0
23	+	3 0	0 18	0 05	+105	+	3	+	0
24	+	1 0	0 19	0 08	+ 80	+	12	0	0

RSR, Regular sinus rhythm
†Deep S in V and V

5 12 and 14) The QRS duration was normal in all patients except for 1 (Patient 10) The mean QRS axis in the frontal plane ranged from +15 degrees to +150 degrees. The typical rSR pattern found in ASD was present in all patients except for 1 (Patient 11) Right ventricular hypertrophy[4] was diagnosed in 7 patients (Patients 1 2 6 8 10 11 and 18)

Phonocardiographic findings Table III summarizes the phonocardiographic findings obtained from the analysis of the first heart sound before and after surgery The amplitude of the tricuspid (T_1) and mitral (M_1) component of the first heart sound was measured in each patient at the apex. The result of such measurement was expressed as a ratio (T_1/M_1) This was done in order to compare the changes in amplitude of both components of the first heart sound before and after surgery irrespective of the calibration of the phonocardiographic instrument. Before surgery 18 of 24 patients had a T_1/M_1 ratio greater than 1 3 patients (Patients 14 18, and 23) had the ratio equal to 1 and only 3 patients (Patients 6 8 and 15) had the ratio less than 1 After surgery the ratio became less than 1 in all but 2 patients (Patients 17 and 21) in whom it was equal to 1 (Fig 1) This, however still represented a decrease in T_1/M_1 In 2 patients (Patients 8 and 15) the Q T_1 interval was more than 0.12 sec however no ejection clicks were identified in either patient. The splitting of the first heart sound (corrected for heart rate) did not change significantly after the surgical procedure (Fig 2) Their value ranged from 0 03 to 0 06 sec. before surgery and from 0 01 to 0 06 sec. after surgery

Discussion

It is known that a loud first heart sound at the apex is frequently found in patients

Table III *Summary of phonocardiographic findings of the first heart sound*

Patient No.	Time interval between surgery and follow-up phonocardiogram	T_1/M at pcr		Q-M interval (sec.)		Q-T interval (sec.)		$\frac{M_1-T}{\sqrt{RR}}$ (sec.)*	
		pre-op	post-op	pre-op	post-op	pre-op	post-op	pre-op.	post-op
1	2 wk.	1 3	0 7	0 06	0 06	0 10	0 09	0 05	0 05
2	2 mo.	2 0	0 7	0 06	0 05	0 09	0 08	0 04	0 04
3	6 mo.	1 6	0 9	0 06	0 06	0 10	0 10	0 05	0 05
4	2 mo.	1 8	0 9	0 05	0 05	0 08	0 08	0 04	0 04
5	6 mo.	2 0	0 7	0 06	0 06	0 10	0 09	0 06	0 04
6	1 10/12 yr	0 6	0 5	0 06	0 05	0 09	0 08	0 04	0 04
7	1 8/12 yr	1 7	0 8	0 05	0 07	0 09	0 10	0 05	0 03
8	11 mo.	0 8	0 7	0 09	0 10	0 13	0 14	0 05	0 04
9	5 yr	1 5	0 5	0 05	0 04	0 09	0 07	0 05	0 04
10	2 wk.	1 7	0 8	0 07	0 06	0 10	0 08	0 05	0 03
11	3 wk.	1 1	0 9	0 05	0 04	0 08	0 07	0 04	0 04
12	2 mo.	2 0	0 7	0 06	0 04	0 09	0 09	0 03	0 06
13	2 mo.	1 6	0 9	0 04	0 04	0 08	0 09	0 04	0 06
14	5 wk.	1 0	0 8	0 04	0 06	0 08	0 08	0 05	0 03
15	1 1/2 mo.	0 9	0 9	0 08	0 06	0 12	0 09	0 05	0 05
16	6 mo.	1 7	0 8	0 05	0 06	0 08	0 09	0 03	0 03
17	4 9/12 yr	2 0	1 0	0 05	0 06	0 09	0 08	0 06	0 02
18	1 mo.	1 0	0 5	0 05	0 08	0 08	0 12	0 04	0 05
19	1 wk.	1 3	0 9	0 07	0 07	0 10	0 11	0 04	0 03
20	2 mo.	1 8	0 8	0 05	0 05	0 09	0 09	0 05	0 04
21	2 wk.	1 9	1 0	0 06	0 05	0 09	0 08	0 04	0 04
22	1 mo.	1 3	0 8	0 05	0 05	0 09	0 075	0 04	0 01
23	3 wk.	1 0	0 8	0 05	0 06	0 08	0 09	0 04	0 04
24	2 1/2 mo.	2 0	0 6	0 07	0 06	0 09	0 08	0 03	0 03

*Splitting of the first heart sound corrected for heart rate.

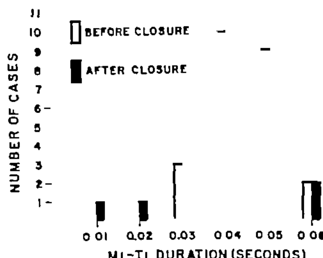


Fig. 2. Distribution of the splitting of the first heart sound corrected for the heart rate $\frac{M\ T}{\sqrt{RR}}$ before and after closure of atrial septal defect.

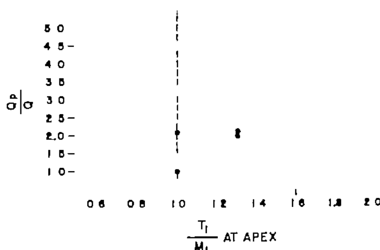


Fig 3 The relation between T /M ratio at apex and Qp/Qs ratio of hemodynamic data shows no positive correlation

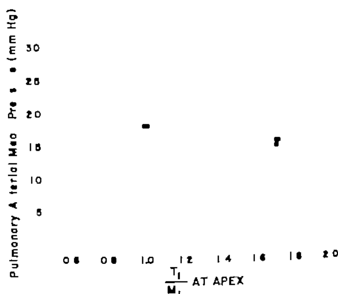


Fig 4 The relation between T_1/M_1 ratio at apex and mean pulmonary artery pressure shows no positive correlation.

with uncomplicated atrial septal defect [3-7] Leatham and Gray[3] and Lopez and coworkers demonstrated that this was produced by an abnormally loud tricuspid component of the first heart sound transmitted to the apex. As a result of this, the normal intensity relationship between the mitral and tricuspid component is reversed and the tricuspid component becomes louder than the mitral component

The present study confirms those previous findings and demonstrates that the atrial septal defect was solely responsible since the tricuspid component became normal in all patients after surgery (Fig 1).

In order to determine if the increased intensity of the tricuspid component was dependent on the size of the left to right shunt it was decided to correlate the T_1/M_1 ratio with the indexed size of the shunt Qp/Qs. As shown in Fig 3 no positive correlation was found

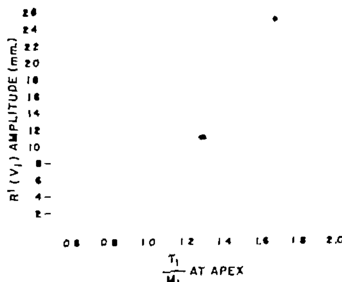


Fig. 5 The relation between T_1/M_1 ratio at apex and amplitude of R (V) in electrocardiogram shows no positive correlation

The finding of pulmonary hypertension in 3 of the children studied (Patients 2 11 and 21) suggested the possibility that a loud T could be related to the pulmonary artery pressure. In order to evaluate this possibility the mean pulmonary artery pressure was correlated to the T_1/M ratio (Fig 4) No positive correlation was found Since all the patients had normal pulmonary vascular resistance, the pulmonary hypertension found was most likely related to increased pulmonary flow The finding that T_1 was of greater amplitude than M at the apex even in the presence of a small left to right shunt is quite significant since it is in this situation where other auscultatory signs are inconsistent in atrial septal defect.

The possibility of a relationship between the intensity of T and the presence of right ventricular hypertrophy was explored This was done in order to investigate if closer proximity of the tricuspid valve to the apex secondary to right ventricular hypertrophy was the cause for it The T_1/M ratio was correlated to the amplitude of the R from precordial Lead V As demonstrated in Fig 5 no positive correlation was found Furthermore, the fact that T_1 became smaller than M in amplitude soon after surgery in all patients with right ventricular hypertrophy (Patients 1 2 10 11 and 17) except 1 (Patient 6) favors the idea that some other mechanism is responsible for it.

An interesting finding in this study similar to that reported by Castle in regard to the second sound was the lack of correlation between the size of the left to right shunt and the splitting of the first sound Moreover no significant changes in the splitting of this sound was found before and after surgery (Fig 2) (Table III) a finding previously reported by Eisenberg and Hultgren. Probably in order to maintain a normal pulmonary flow the right ventricle responds to an increased volume load by increasing the force of contraction and the speed of ejection The net result as a consequence is increased velocity of the pulmonary flow and only slight prolongation of its mechanical systole.[8] This would favor the idea that sudden closure of the tricuspid valve is the main factor responsible for a loud T_1 Accordingly this would explain why a loud T is found even in patients with small shunts

Since a T louder than M at the apex is rarely found in cardiac conditions other than atrial septal defect [9,14] its finding should be strongly suggestive of the presence of this congenital defect. Therefore by comparing the amplitude of both com

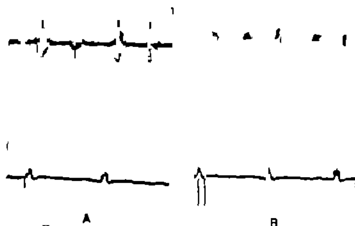


Fig 6 *A* Typical preoperative phonocardiogram recorded at the apex in Patient 5 Note splitting of the first heart sound with increased amplitude of T (T_1/M_1 ratio > 1). *B* Phonocardiogram recorded in the same patient 6 months after closure of atrial septal defect showing splitting of the first heart sound with T_1 smaller than M_1 (T_1/M_1 ratio < 1).

ponents of the first heart sound at the apex as a routine phonocardiographic procedure, the physician has a valuable sign for the diagnosis of atrial septal defect and of the success or failure of surgical closure in the early postoperative period A typical preoperative phonocardiogram of one of the children studied is shown in Fig 6 (Patient 5)

Summary

The pre- and postoperative phonocardiograms of 24 children with uncomplicated atrial septal defect (ostium secundum type) were analyzed. The amplitude of the mitral (M_1) and tricuspid (T_1) components of the first heart sound were measured in each patient at the apex prior to surgery It was found that in 18 of the 24 children studied (75 per cent) T_1 had higher amplitude than M_1 at the apex (T_1/M_1 ratio > 1) Three out of 24 children (12.5 per cent) had equal T_1 and M_1 amplitudes (T_1/M_1 ratio = 1) and 3 (12 5 per cent) had T_1 amplitude less than M_1 (T_1/M_1 ratio < 1) No positive correlation was found between the T_1/M_1 ratio and the size of the left to right shunt mean pulmonary artery pressure right ventricular hypertrophy and/or degree of splitting of the first heart sound After surgery the T_1/M_1 ratio became less than 1 in 22 children and equal to 1 in 2 children A T_1 higher than M_1 at the apex is a sensitive index of atrial septal defect since this finding was present even in the presence of a small left to right shunt. Routine phonocardiographic measurement of the amplitude of both components of the first heart sound at the apex is recommended.

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The first heart sound in atrial septal defect

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Several authors have reported a marked splitting of the first heart sound in atrial septal defect (ASD).[1] This splitting has been explained as due to a marked accentuation of the normal tricuspid component, and so far no other explanation has been advanced.

Graphic studies originating in our laboratory have proposed a different interpretation of the various components of the normal first heart sound. Three groups of vibrations were recognized: the first two (a and b) originating in the left ventricle and the third (c) in the aorta. It was also suggested that clinical cases presenting a loud vibration in early systole had either an accentuation of the *c* component (aortic ejection sound) or the occurrence of a new vibration without physiologic correlates (pulmonary ejection sound). The latter would be closer to the beginning of the first heart sound than the former and has been described in a variety of conditions including pulmonary stenosis, pulmonary hypertension, idiopathic dilatation of the pulmonary artery, and ample shunts causing an increase of pulmonary flow.

In view of this change in interpretation that shifts the emphasis away from the right heart and minimizes valvular factors, it was considered that a new clinical study of patients with atrial septal defects would be of interest.

Material and methods

Our study was made in 18 subjects, 12 females and 6 males ranging in age from 14 to 39 years.

Following a clinical and electrocardiographic study, phonocardiograms were recorded with the subject in the supine position using a Sanborn multichannel apparatus with high pass filters (modified in this laboratory[11]). Catheterization of the right heart was performed in routine fashion under mild sedation.

Sixteen out of 18 patients had an atrial

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septal defect of the *secundum type* while ? had an *ostium primum*. Minimal pulmonary stenosis was observed in ? patients dextrocardia right-sided aortic arch and partial anomalous venous return were documented in one patient each.

In all cases, the three components of the first sound were looked for and the following graphic measurements were made (1) interval between Q and the three components of the first heart sound (Q-Ia, Q-Ib, Q-Ic) (2) intervals between components of the first heart sound (Ia-Ib and Ia-Ic intervals) (3) interval between Q and the onset of pressure rise in the right ventricle and in the main pulmonary artery respectively and (4) ratio of amplitude of the components of the first heart sound $\left(\frac{Ia}{Ib} \text{ and } \frac{Ia}{Ic}\right)$

In addition comparison was made in 5 cases between the timing of the main components of the first heart sound and the first derivative (dp/dt) of pressure of either ventricle.

Measurements of the first heart sound were made in tracings recorded with one of three filters (50, 100, or 200). The paper speed was 100 msec. The delay in transmission of pressure and sound waves by catheters No. 6 or 7 was tested in 2 experiments and ranged from 5 to 10 msec (similar to the value obtained by Köhler[4]). Therefore the data comparing sound phenomena to pressure rise were corrected for this delay by subtracting 10 msec.

Results

The electrocardiograms revealed sinus rhythm at rates ranging from 68 to 90 beats per minute in all subjects and incomplete right bundle branch block in cases.

Two out of 18 patients had elevation of pulmonary artery pressure (one had 34/7 and one 80/35) while the others had normal pulmonary artery pressure. The Ia-Ib interval ranged from 20 to 55 msec (average 31.7 msec). In 2 of the 18 patients the interval was slightly prolonged (50 to 55 msec.) while the normal interval is from 25 to 40 msec.

The Ia-Ic interval ranged from 35 to 90 msec (average 73.0 msec.) and was prolonged (90 msec.) in 2 cases over the normal range of 50 to 70 msec.[17]

The Q-Ia interval ranged from 55 to 80 msec (average 68.1 msec.). This average is definitely prolonged over the normal Q-Ia interval which is close to 50 msec. The Q-Ib interval ranged from 85 to 115 msec (mean 99.8 msec.). The Q-Ic interval ranged from 120 to 150 msec (mean 141.1 msec.). The interval Q onset of pressure rise in the right ventricle varied between 40 and 70 msec with an average of 49.7 msec. Corrected for catheter delay the average was 39.7 msec. The interval Q onset of pressure rise in the pulmonary artery ranged from 75 to 110 msec (mean 90.0 msec.). Corrected for catheter delay this average interval was 80.0 msec.

The time relationship between the Q-Ib interval and the Q onset of right ventricular pressure rise was 60.1 msec indicating that the b component of the first heart sound *followed* the onset of right ventricular pressure rise by over 60 msec. The time relationship between the Q-Ib interval and the Q onset of pulmonary artery pressure rise corrected was such that the pressure rise *invariably occurred before Q-Ib*.

Comparison between components of the first heart sound and the first derivative of pressure of either ventricle showed a close relationship of the two components (a and 1) of the first heart sound and the waves of the first derivative of left ventricular pressure while none was found with the first derivative of right ventricular pressure.

The ratio of amplitude of the three components of the first sound showed that the Ib component of the first sound was abnormally high in 13 of the 18 patients. The Ia component of the first sound was the largest in 2 of the cases, and the Ic component of the first sound was the largest in ? other patients. One case had all components of the same amplitude.

Discussion

The interval between the Q wave of the electrocardiogram and the first component of the first heart sound (Ia) was often prolonged in our cases so that an average mean Q-I of 68.1 msec was found. The reason for this fact is still unclear.

The interval between the *a* and the *b* components of the first heart sound was normal and that between *a* and *c* was prolonged only in 2 cases.

The *b* component was the special object of this study because of the contention that it is related to tricuspid valve closure [1] In our series the interval between the Q wave of the electrocardiogram and the *b* component of the first sound had an average duration of 99 8 msec. (Table I)

The interval between the Q wave and the onset of pressure rise in the right ventricle (corrected for catheter delay) was 39 7 msec As closure of the tricuspid valve either precedes or is simultaneous with the onset of right ventricular pressure rise it can be assumed that the average interval Q tricuspid valve closure would be in the range of 40 msec (Table I) This is longer than the average quoted interval for dogs (20 msec) [1] a fact that might be explained first by species difference and second by greater blood volume in the right heart. This interval is nearly 50 msec shorter than that between Q and the b component of the first sound thus excluding that the latter has any connection with the valvular event.

The study of the interval between Q and onset of pressure rise in the pulmonary artery shows that the latter is 80 msec. (Table I) This is much longer than the average quoted interval for normal dogs (30 msec) [3] a fact which is again explained by species difference and by greater blood of the right heart.

A comparison between the two (a and b) main components of the first heart sound and the first derivative of pressure of either ventricle has shown the following facts. (1) There is a coincidence between the *b* component and either a change of slope or a secondary wave of the *left* ventricular first derivative this was described in the normal dog by Shah and associates[4] and is commonly observed in normal man (2) No coincidence was found between this component and the peak (or peaks) of the *right* ventricular first derivative this was dramatically evident in a case with right bundle branch block having a marked delay of right ventricular contraction

In regard to amplitude, the *b* component was the largest in 13 out of 18 cases. However this is not unusual in normal subjects as shown by our routine tracings and cannot be accepted as an abnormal phenomenon.

In conclusion our studies of 18 cases of atrial septal defect have shown no recognizable connection between the *b* (or second) component of the first heart sound and the closure of the tricuspid valve.

Summary

An electrocardiographic phonocardiographic, and right-sided cardiovascular pressure study was made in 18 cases of atrial septal defect. The study was primarily concerned with the various components (a b and c) of the first heart sound (I) and their relationship to the dynamic events of the right heart. The following facts were ascertained. (1) The average Q-Ia interval is prolonged. (2) The Ia Ib and Ia Ic intervals are normal (3) The Q-Ib interval is much longer than the Q-right ventricular pressure rise. (4) The Q-Ib interval is even longer than the Q-pulmonary artery pressure rise. (5) Both the *a* and *b* components have a close re

Table I Average intervals (msec) between electrocardiographic and phonocardiographic and pressure events in atrial septal defect

Interval between onset of QRS and sound component		Q–I 68 1		Q–Ib 99 8	Q Ic 141 1
Interval between onset of QRS and onset of pressure rise	39 7 Q-pressure rise RV (corrected)		80 0 Q-pressure rise P-A (corrected)		

lationship with the secondary accidents of the tracing of the first derivative (dp/dt) of left ventricular pressure.

As a result of these measurements, the Ib component should be considered as unrelated to closure of the tricuspid valve

Other considerations are made in regard to the amplitude of the various components of the first heart sound in atrial septal defect

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The coronary attack: Concepts on its etiology and hemodynamic management

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The cornerstone of the natural history of the coronary attack would still appear to be the concept of occluded coronary arteries and this concept generally forms the basis of the modern therapeutic approach. This hypothesis, however, fails to explain the finding by pathologists of myocardial infarction with no concomitant thrombosis or even occlusion of the coronary vessels.

As recently as 1967, Bondurant[1] in referring to myocardial infarction as a "well of ignorance" has stated, "Even the classic formulation that coronary occlusion, thrombotic or otherwise, precedes ischaemic necrosis . . . is now clearly inadequate." In December, 1968, Kagan and associates[2] in an autopsy study found a significant percentage (25 per cent) of 176 instances of large fresh myocardial infarctions without thrombosis or other occlusion of the extramyocardial coronary arteries. They showed a significantly higher incidence of early death (within 6 hours) in the infarcts not associated with occlusion.

A re-examination of the natural history of the coronary attack is therefore essential with special reference to the following: (1) If coronary occlusion is not the invariable precipitant of the attack, what other precipitants may there be? (2) If there are other precipitants, is an infarction the inevitable late sequel? (3) Is there incontrovertible evidence that when an infarction is associated with a thrombosis it is always preceded by vascular thrombosis and not vice versa? Is it not feasible that there is a slowing down of the blood flow to a portion of dead heart muscle with penultimate thrombus formation?

In view of the above, we have instituted a fundamental research program in which the coronary attack has been investigated in the light of the principle of conservation of energy.[3] The basic viewpoint is that since the organ involved, the heart, is a pump and hence a utilizer of energy, it must be subject to the laws of physics. (It must be particularly borne in mind that it is a unique pump in that its energy source arises [at the coronary ostia] from its output flow rate.)

There may well be reaction from some readers to the application of these laws of physics, generally derived from experiments on inanimate substances, to living tissue. The answer to this outlook, involving as it does a great number of fundamental philosophical attitudes, cannot be given in this paper. Instead the reader is referred to Dr. Asimov's book, *Life and Energy*,[4] in which the reasons permitting the applica-

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tion of the quantitative laws of physics to animate matter are detailed at length

As the basis of our investigation two original equations have been used These relate first to the mechanical efficiency of the pumping left ventricle in terms of its stroke volume, and second to the systemic flow rate in terms of variables not involving the aortic pressure.[9] These are presented as Equations 2 and 3 of this paper From these equations a therapeutic rationale has been derived for the management of the coronary attack. In addition the action of the cardiac drugs utilized is shown to be capable of visualization on the pressure volume (P V) diagram of the left ventricle (Fig 6) [11]

The object of this paper is to present this rationale and its results as applied to 41 patients since the establishment in September 1968 of the Department of Cardio-Dynamics at Addington Hospital Durban

Definition of a coronary attack

We recognize a patient as experiencing a coronary attack if he or she gives a history of prolonged and intense chest pain (severe enough to require the administration of opiates) together with electrocardiographic (ECG) features to be discussed in detail below but primarily exhibiting S-T segment displacement (depression or elevation) with or without a falling R wave We also include cases presenting in cardiac shock with similar ECG abnormalities, but without preceding pain e g post operative cardiac shock.

Material and methods

The 41 patients mentioned above all presented with a coronary attack as defined above 39 presenting with precordial pain and as postoperative cardiac shock both groups associated with characteristic ECG changes

Deaths Five of the above 41 patients died and autopsy revealed that 2 of these were noncardiac deaths. The first had diabetes and bilateral pneumonia (each lung weighing 1 000 grams at postmortem examination) There was evidence of an old infarction but no fresh infarction was demonstrable Death took place in 5 days.

The second noncardiac death was due to postoperative pulmonary embolism after she had been admitted to our unit following a cardiac arrest, was restored hemodynamically and was transferred back to the surgical ward in a satisfactory condition She was, unfortunately overtransfused and died shortly afterwards

There were 3 cardiac deaths in 41 patients. The first patient, age 51 died 12 days after admission the second patient age 65 also died 12 days after admission and the third patient, age 71 died 5 days after admission. There have been no cardiac deaths in the last 24 admissions to the unit (over the past 2 months)

Age distribution The mean age was 63 years, and the age distribution was as follows under 40 years old 0 patients 41 to 50 years, 6 patients 51 to 60 years, 10 patients 61 to 70 years, 14 patients 71 to 79 years, 9 patients 80 years and older 2 patients.

There were 10 females and 31 males, with a degree of selectivity in favor of males because of accommodation and staff problems.

ECG analysis

ARRHYTHMIAS ON ADMISSION Twelve cases (6 auricular fibrillation 2 premature ventricular systoles, 1 heart block (A V dissociation) 2 ectopic ventricular foci and 1 nodal tachycardia) presented with arrhythmia.

ECG ABNORMALITIES OF THE QRS COMPLEX These according to our interpretation detailed in the section below are shown in Table I

Thirty three patients left the hospital with inverted T waves suggesting that an infarct had developed.

CONGESTIVE CARDIAC FAILURE. Fourteen patients presented with superadded cardiac congestive failure on admission.

HYPOVOLEMIA Six patients were assessed as hypovolemic, 5 of whom were considered to be iatrogenic (dehydrated by diuretics prior to admission) and 1 due to excessive vomiting probably secondary to alcoholism.

CARDIAC SHOCK. Eight presented with cardiac shock (systolic blood pressure below 70) and a further 4 developed cardiac shock after admission (1 following a second dose of propranolol 1 induced by excessive lignocaine 1 went into cardiac shock after using a commode and 1 immediately after

Table I

Data	*Type of abnormality**				
	S-TD	*S-TE*	*S-TE and DR*	*D→E*	*D→E→DR*
No of cases	29	6	4	1	1
For example see	Cases A and B Fig 1( )	Cases C and D Fig 1( )	Cases C and D Fig 1 (ii) and (iii)	Case C	Case C

*S-TD = S-T depression S-TE = S-T elevation; S-TE and DR = S-T elevation followed by dipole reversal D→E depression going to elevation D→E→DR = depression going to elevation, followed by dipole reversal.

the patient had been listening to a rugby football match on the radio—this latter case developed cardiac arrest, but survived 3 days thereafter)

Enzyme studies The survivors included 1 with an SGOT of 400 Karmen units 2 with SGOT's of between 300 and 400 Karmen units 3 with SGOT's of between 200 and 300 Karmen units 7 with SGOT's of between 120 and 200 Karmen units. Of the remaining 23 survivors, 18 had raised SGOT s of less than 120 and 5 were not recorded

Electrocardiographic considerations In 1927 Craib[3] recorded a QRS complex by stimulating one end of a strip of cardiac muscle immersed in a saline bath with 2 electrodes, A and B placed over the strip and connected to a galvanometer (*G*) (Fig 1) He was able to show that a Q wave developed as the pathway of the dipole approached electrode A and an S wave developed as the dipole s pathway moved past electrode B The Q and S waves were not able to be recorded if the electrodes A and B were placed beyond the limits of the muscle strip (as in Standard Lead I)

In 1963 Posel applied the principles of the Craib traveling dipole to the human heart and was able to reproduce Craib s findings by placing the electrodes of any standard lead at approximately V_{4R} and V_4. The V_{4R} lead placing was moved inward till a Q wave was recorded and the V_4 lead adjusted inward slightly till an S wave was recorded. Posel was able to show that the theory of Craib s traveling dipole hypothesis was correct from a mathematical viewpoint as opposed to Einthoven s pivoting dipole hypothesis. Thus the current appears to pass through the heart as if it is traversing a strip of muscle stretched transthoracically from right to left in a straight line.

In our studies of the coronary attack, we have used this transthoracic lead extensively and have found it to be capable of yielding no less and often more information than the conventional Wilson twelve-lead system

If the pathway of the dipole is obstructed by chemical or anatomical damage near the end of its passage from R to L (see Fig 1 i) then we record S-T depression. If the obstruction extends proximally (Fig 1 ii) then S-T elevation is recorded (thus we have found in the more severe attacks with higher SGOT's) and if there is gross obstruction to the dipole s pathway (Fig 1 iii) then we have been able to observe in serial series a reversal of the pathway of the dipole (from left to right) Examples of these 3 types of ECG abnormality are shown in Cases A, B, C and D The dipole reversal shown in Cases C and D reveals that the so-called Q wave in full thickness infarcts (of present terminology) may be viewed as R wave in reverse

The ECG may be regarded as an accurate transducer capable of displaying accurately the nature of the prevailing myocardial metabolism. We base this deduction on the experimental work reported by Scherf and Brachfeld[4] and corroborated by Roesler and associates in vivo

Summary of typical case histories

Case A: SGOT two days after admission ... *Farmers* ... G. N a 80-year-old man ... sudden and intense chest pain at 9 P.M. on ...

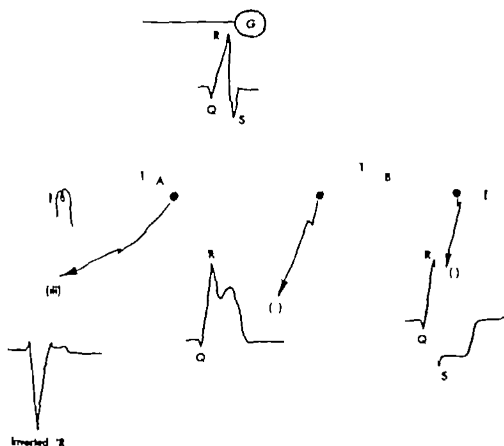


Fig. 1. The Crafb travelling dipole.

1968. Fig. 2, *A* shows the ECG taken at 11.15 A.M. at his home when he was pale and agitated and in severe drenching sweat, with blood pressure of 170/100 mm. Hg and pulse rate of 43 per minute. Signs of heart block with A-V dissociation are seen to be present. He was transferred to Addington Hospital by ambulance after the administration of 50 mg. pethidine and 50 mg. Valoid.

Fig. 2, *B* shows the ECG on admission to the unit; he was sweating profusely, being cold and clammy with blood pressure of 220/100 mm. Hg. In view of the bradycardia, digoxin therapy was not considered, and the inotropic drug chosen was isoproterenol, 8 ampa. per liter of 5 per cent dextrose/water commencing at 4 drops per minute. His extremities became warm by 5.30 A.M. Nov. 6. To counter rising blood pressure of 180/70 mm. Hg at 10 P.M. that night, methyldopa 250 mg. was given orally at 10:20 P.M., again at 11.20 A.M., and again at 1.15 A.M., until by 6 A.M. on Nov. 7 the blood pressure fell to be within our desired range, 185/60 mm. Hg.

Fig. 2, *C* shows the ECG on Dec. 2 when the blood pressure was 110/70 mm. Hg. A remarkable improvement is evident and it is normal apart from a slur in the RS-T segment.

Fig. 2, *D* shows the ECG on Dec. 14 when the patient had been ambulatory for 7 days. The blood pressure was 114/86 mm. Hg. He was discharged on Dec. 16 and has maintained excellent progress.

We regard this case as an example of our postulate of the prophylaxis of an infarct. Despite the high SGOT value and the advanced age of the patient, there was no evidence of an inverted T wave on discharge. On this basis we feel that correct hemodynamic action, instituted early enough, is capable of averting an infarction.

Case B. SGOT two days after admission 85 Karmen units. As a further example of the prophylaxis of an infarct, we offer the case of W. B. C., 75-year-old man who developed severe chest pain at 7 A.M. on Dec. 5, 1968. Fig. 3, *A* shows the ECG on admission to the unit at 11.30 A.M. in severe pain, pale, and sweating profusely with blood pressure of 220 systolic. Since atrial fibrillation is shown with an irregular ventricular pulse rate in the vicinity of 150 per minute, the patient was given 1 mg. digoxin intravenously immediately.

At 12 noon the ventricular rate had decreased to 50 per minute, when methyldopa 250 mg. was given orally and isoproterenol therapy commenced. Fig. 3, *B* shows the ECG at 1.25 P.M. when the blood pressure was 110/65 mm. Hg and the ventricular rate 50 per minute. Atrial flutter is now evident, with low voltage P waves. His extremities remained cold and pale.

*Ampa. ... ampules, each containing 20 mg./ml.

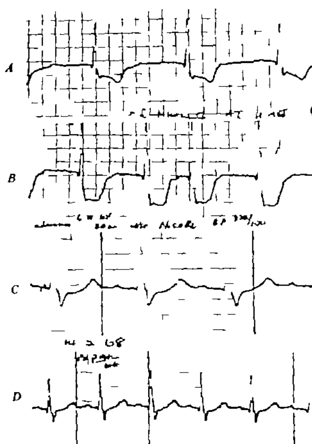


Fig 2 A D Case A See text for explanation.

Fig 3 C taken at 2 10 P.M. shows for the first time the return to normal sinus rhythm with blood pressure of 120/60 mm Hg. His extremities remained cold.

Fig 3 D was taken at 3 35 P.M. when the isoproterenol therapy was 12 amps per liter at 16 drops per minute. The blood pressure was 124/60 and extremities were warm for the first time since admission 4 hours earlier.

Fig 3 E taken at 10 A.M. on the Dec 7 shows an almost isoelectric S-T segment. The blood pressure was 110/60 mm Hg with isoproterenol therapy 8 amps per liter at 6 drops per minute.

Fig 3 F shows normal ECG at the time of discharge 19 days after admission. The blood pressure was 110/50 mm. Hg and the patient was ambulatory.

Case C. SGOT two days after admission 400 Karmen units H. S. R. 49-year-old man, was seen by one of us (N. McE. L.) at an outside hospital 5½ hours prior to admission. He gave a 24 hour history of intense chest pain only partially controlled by analgesics. The ECG (Fig 4 A) showed a low R wave of 9 mm. and high T wave of 8 mm. and early S-T depression. He was seen in the same hospital 4 hours later when the ECG (Fig 4 B) showed marked change to S-T elevation with fall of the R wave to 3 mm. The blood pressure was 140/90 mm. Hg. Arrangements were made to transfer him to our unit at Addington. On admission he was pale, sweating, and extremely agitated. He had a persistent cough. He was given 500 mg methyldopa orally and 1 mg digoxin intravenously. Isoproterenol was withheld at this stage because of the intense agitation and tachycardia suggestive of an adrenergic discharge and was only commenced (10 amps per liter) 1½ hours after admission to the unit when the blood pressure [illegible] 120/80 mm Hg (pulse 100 per minute). Three hours later the blood pressure was still 120/80 the pulse was 103 per minute and the ECG (Fig 4 C) showed a reduction in S-T elevation [illegible] break in the S-T origin (also alternans). [illegible] extremities were recorded then

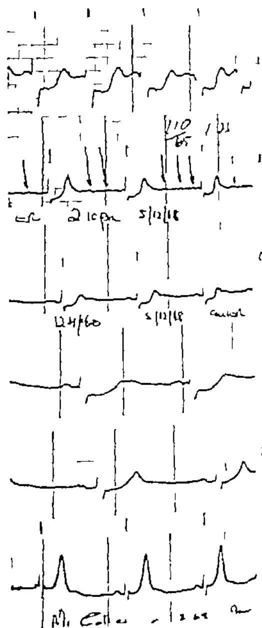


Fig 3 A F Case B See text for explanation

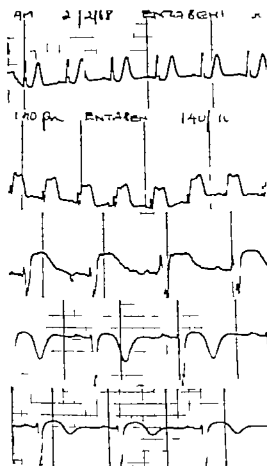


Fig. 4. *A-D*. Case C. See text for explanation.

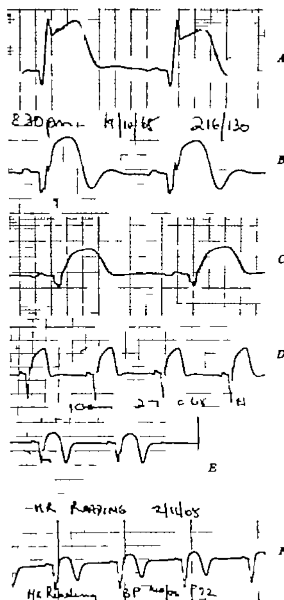


Fig. 5. *A-F*. Case D. See text for explanation.

time. Hydrocortisone 200 mg. per liter was added to the therapy on the morning of day 2 and 12 hours later dipole reversal was observed for the first time (Fig. 4, *D*). Thereupon a further dose of digoxin (0.5 mg. intravenously) was administered. On day 3 the patient was well clinically and the isoproterenol was gradually reduced in concentration and rate and finally discontinued on the sixth day following admission. Fig. 4, *E* shows the ECG on discharge 19 days after admission. Note the persistence of dipole reversal with the development of an inverted T wave. He has remained well on follow-up, his only medication being Librium 10 mg. three times a day.

Case D. SGOT one day after admission 295 Karmen units. F. J. R., aged 50, is another example of the development of dipole reversal from S-T elevation. Fig. 5, *A* on admission shows marked S-T elevation. Fig. 5, *B* shows a falling R wave. Fig. 5, *C* shows great reduction of dipole strength and dipole reversal. Fig. 5, *D* shows slight strengthening of dipole but still marked S-T elevation and dipole reversal persisting. Fig. 5, *E* shows reduction of S-T elevation and the appearance of an inverted T wave, and Fig. 5, *F* is the ECG on discharge 39 days after admission.

This patient presented with severe pain and agitation and was at all times aggressive and emotional. The blood pressure on admission was 170/110 mm. Hg and pulse 76 per minute. The blood pressure rose in 7½ hours to 210/130 mm. Hg (pulse 68 per minute). The pain and agitation persisted for 48 hours by which time the blood pressure fell gradually to 144/88 mm. Hg. He was treated initially with isoproterenol (4 ampules per liter), which had to be stopped temporarily. Because of the intense agitation, propranolol (10 mg. orally) was reluctantly administered. He was also given hydrocortisone (200 mg. per liter) shortly after admission, and when the blood pressure rose to 210/130 mm. Hg he was given methyldopa 250 mg. every 8 hours,

which ppeared to reduce the blood pressure gradually. As the dipole strength fell (see Fig 5 C) he was given intravenous digoxin 0.5 mg. repeated twice daily and from then on his convalescence proceeded gradually and uneventfully. He was discharged 39 days after admission and remains well on follow-up. It has been found that he requires 500 mg methyldopa every 8 hours to keep th blood pressure within normal range.

Fundamental concepts

Since the heart takes up energy and does work it must be regarded as a pump and must therefore operate according to the basic laws of physics. One of us (K. P.) has recently examined[7] the coronary artery system in the light of the principle of conservation of energy. In this analysis, attention is focused on concepts such as input energy delivered to the myocardium (by the coronary artery system) the output pumping work accomplished by the left ventricle (LV) (the product of the mean aortic pressure and the cardiac output flow rate) and the mechanical efficiency (ME) with which this work is achieved.

According to the principle of conservation of energy we thus have

$$\text{ME of myocardium} = \frac{\text{output pumping work/min.}}{\text{input energy supply to myocardium/min.}} \quad (1)$$

and this efficiency is always less than 100 per cent.

In the above equation clinicians to date would appear to have focused all their attention on the input energy to the heart whereas this must be regarded as the dependent variable. The independent variable is the output work that is set to the left ventricle at any given moment and over any given period of time. In other words the heart will take up its energy requirements according to the load it is set. It cannot, according to the laws of physics, be made to take up more energy than it requires in relation to its own index of efficiency. In this light, the concept of the use of coronary vasodilators is untenable.[7] For example it has been shown that an in vitro coronary artery will constrict as will any other artery when bathed in a solution of noradrenaline but an in vivo coronary artery dilates in a patient to whom noradrenaline is administered because the heart has been set a greater work load by the noradrenaline causing peripheral constriction.

Postulated etiology of the coronary attack

We postulate that a coronary attack is that set of circumstances which comes about when the aerobic input energy to the myocardium is inadequate (in terms of the principle of conservation of energy) for the pumping work performed at that moment by the left ventricle. (We have deduced this from the presence of S-T segment deviation of the ECG together with our interpretation of the ECG as an energy transducer whereby such S-T deviation indicates the presence of anaerobic metabolism.)

Once this aerobic input energy deficiency has developed resort has to be made by the myocardium to a supplementary and hence anaerobic energy supply (possibly from anaerobic glycolysis). We thus postulate that it is this state of what we term myocardial anaerobiosis, which if it is of sufficient severity or persists sufficiently long causes the coronary attack with all its associated clinical biochemical and electrocardiographic features.

We postulate further that this anaerobiosis if it continues for sufficiently long results in the development of an infarction. Rapid reversal back to aerobic metabolism should therefore be capable of averting an infarction. Using the equation for the conservation of energy

$$\text{Myocardial mechanical efficiency} = \frac{\text{output pumping work}}{\text{input energy supply}}$$

it follows that a coronary attack may be precipitated by one or more of the following conditions

1 For the ruling value of the myocardial mechanical efficiency an output work load of the pumping left ventricle exceeding the available aerobic input energy supply. This may in turn be subdivided into two conditions (a) excessive left ventricular pumping work in the presence of normal input aerobic energy supply (e.g. hypertensive cases submitted to sudden increase of work load) (b) inadequate input aerobic energy supply in the presence of a normal output pumping work and

tion. The condition is recognized as encompassing not only the thrombotic element of the past, but also anemia hypoxia and diabetes.

2. For the ruling value of the left ventricular output pumping work, a value of the myocardial mechanical efficiency too low to permit the achievement of this work by aerobic means.

An additional finding of importance with regard to the etiology of the coronary attack is condition 2 above particularly with regard to the role of noradrenaline in this connection in the fight or flight mechanism. Sarnoff and associates[9] have shown in great detail in the isolated heart preparation that, apparently for reasons as yet unexplained by the biochemist, infusion of noradrenaline into the myocardium leads to a great reduction in mechanical efficiency On this basis we are of the opinion that too little attention has been paid to the manner in which episodes of either prolonged or intense emotional stress can be regarded as a precipitant of the coronary attack.

Fundamental concepts in therapy

On the basis of the above postulated etiology of the coronary attack, it is seen that therapy in the coronary patient must attempt to re-establish an aerobic energy balance between the left ventricular pumping work and the prevailing degree of myocardial mechanical efficiency It is then obvious that this may be achieved by (a) reduction of the prevailing left ventricular pumping work and/or (b) increase in the prevailing myocardial mechanical efficiency

Reduction of left ventricular pumping work The left ventricular pumping work is given by the product of the mean aortic pressure and the cardiac output flow rate. One method of achieving clause (a) above is thus the use of hypotensive agents to reduce the blood pressure against which the left ventricle ejects its stroke volume. On this basis we regularly use the drug methyldopa to decrease the systolic pressure of our coronary patients to a level of some 110 mm. Hg in those instances of pressures presenting above this value. W have experienced no disadvantageous effects of this unloading of the left ventricle procedure in any of our patients to date on the other hand improvement in S-T segment displacement has occurred without fail.

Increase in myocardial mechanical efficiency Therapy in this connection is based on an equation derived by one of us (K. P) regarding the mechanical efficiency of the denervated heart as follows (where k and α are constants)

$$\text{Myocardial mechanical efficiency} = \frac{1}{1 \quad + k(SV)} \qquad (2)$$

This equation shows that the mechanical efficiency increases as the stroke volume increases. Successful therapy in the coronary patient must thus attempt to increase the stroke volume ejected by the left ventricle

The importance of avoiding the state of hypovolemia thus becomes apparent since stroke volume cannot be increased under such conditions Once hypovolemia is corrected the manner in which inotropic drugs can be made to result in such a stroke volume increase has recently been shown.[11] We therefore, use the inotropic cardiac drugs, digitalis and isoproterenol, during the coronary attack. We have used these drugs with consistent success in all cases to date subject to the strict proviso that continual ECG monitoring be used to indicate the correct drug concentration. This latter aspect, which we cannot stress sufficiently is elaborated upon later in this paper

Instances of cardiac shock

It is of interest to point out that despite its immediate clinical recognition as a state of cold and clammy extremities the definition of the state of shock as an instance of systemic flow inadequate for correct tissue perfusion is only of comparatively recent origin Blood pressure is low in a state of shock because the systemic flow is low and not vice versa.

On the basis of the previous reasoning it would appear that one possible interpretation for the occurrence of a state of shock is that whereby the left ventricle finding itself in a state of myocardial anaerobism unloads itself (by devices as yet undetermined) and decreases its cardiac output flow rate. Thus tissue perfusion suffers

while the reduced left ventricular pumping work condition attempts to restore the required aerobic energy balance.

In order to evaluate the required therapy in this instance an equation was derived for the systemic flow rate Q wherein the variable of blood pressure does not feature at all. This arises on the recognition that as the left ventricle is a positive-displacement pump flow causes pressure and not vice versa, as is commonly accepted. The resulting equation may be shown to be

$$Q = \frac{ME \times cor\ AV\ O_2\ diff \times 2.08}{R + R} \qquad (3)$$

Where

Q = systemic flow rate per minute, ME = mechanical efficiency of the pumping LV, Cor AV O diff = coronary arteriovenous oxygen difference, R = systemic resistance, R = coronary artery resistance.

The aim in instances of cardiac shock is to increase Q. The above equation shows that firstly the systemic resistance R must be reduced (resolving the often repeated argument of constrictors versus dilators) and second the stroke volume must be increased. The remarks made pertaining to a stroke volume increase in the previous paragraph thus apply again here, that is the efficacy of isoproterenol and digitalis in instances of cardiac shock is deduced provided that the condition of hypovolemia is avoided in the patient. Because isoproterenol accomplishes both of the required objectives (peripheral dilatation and stroke volume increase) whereas digitalis achieves only the latter the advantage of isoproterenol over digitalis under these conditions is apparent.

The visualization of action of cardiac drugs

The action of the drugs isoproterenol, digitalis, noradrenaline and propranolol are well visualized on the pressure-volume diagram (PV diagram)[11] (Fig 6).

The compliance curve of the left ventricle (LV) as shown in the diagram has the same shape as that of any distensible object e.g. a balloon. Thus, at low pressures the volume increases substantially until the walls take up the tension whe

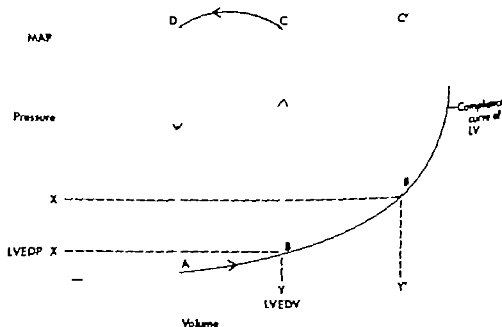


Fig 6 The pressure-volume diagram of the left ventricle.

the pressure rises more precipitously for minimal volume increase. A point is reached where any pressure rise is limited by the volume of the LV beyond which rupture will take place, i.e., the balloon will burst.

The cardiac cycle can be visualized on this diagram without considerations of time. At some point A diastole commences, and at point B the end of diastole is reached at which point the heart is filled with noncompressible blood but the aortic valve is still closed. Here the LV attempts to contract with a resultant rise in intra LV pressure at fixed volume up to point C when the pressure attains the *mean aortic pressure* (*MAP*). The aortic valve opens, there is a slight further pressure rise (depending on the elasticity of the arterial tree) with reduction in volume to point D which is the end of the systole, at which point the pressure falls to point A again at fixed volume for the recommencement of the cardiac cycle.

Point Y is the LV end diastolic pressure (*LVEDP*) and point Y is the LV end diastolic volume (*LVEDV*).

The intra LV pressure rise from B to C has been called the myocardial bearing down ability (MBDA)[11] and can be regarded as an intrinsic property of each individual heart.

It is evident on the PV diagram that for the same MAP a reduction in MBDA (as will occur in a damaged or weak heart) must result in the line BC moving to the right on the compliance curve which will result in the LVEDP rising to point Y and the LVEDV moving to Y', i.e., a damaged or weak heart is an enlarged heart with a raised LVEDP.

The action of various cardiac drugs can be clearly visualized on this diagram. The inotropic drugs such as digitalis, isoproterenol, and noradrenaline will increase the length of MBDA and tend to move the line B C' to the left, thus reducing heart size and lowering LVEDP. Drugs with an opposite action (e.g., propranolol) will reduce the MBDA and thus explain why a patient on the brink of failure will be precipitated into failure by the administration of propranolol.

The inefficacy of noradrenaline in the coronary attack is explained by the fact that not only does this drug reduce mechanical efficiency of the pumping LV but it will raise the *MAP* by vasoconstriction.

The rationale of lowering blood pressure is also clearly evident as this must tend to move the point B' nearer to point B.

Finally, the action of the L auricle which on this diagram must cause the pressure rise from point A to B can be seen to play a much more prominent role in the damaged heart from A' to B' (the development of an atrial gallop is a well-recognized phenomenon of the failing LV). This explains the reason for the high incidence of cardiac arrhythmias in the damaged hearts of patients in a coronary attack, bearing in mind the fact that the electrical conduction tissue traverses the auricles en route from the S-A node to the AV node. It also explains the persistence of arrhythmia problems if attention is not directed primarily towards moving the *MBDA* line to the left as a matter of urgency in the damaged heart. Thus, it is of prime importance in the prophylaxis of arrhythmias in these hearts to lower the *LVEDP*. This can be done by three methods: (1) keeping *MBDA* constant and lowering blood pressure, e.g., methyldopa; (2) keeping blood pressure constant and increasing *MBDA*, e.g., with digitalis; (3) by simultaneously reducing blood pressure and increasing *MBDA*, e.g., with isoproterenol plus methyldopa.

Detailed therapy of the coronary attack

If not seen in his home, the patient is, if possible, met in the emergency room by a specially trained medical officer and nursing sister. A transthoracic ECG is immediately recorded and the following features are evaluated:

A. An attempt is made to categorize the patient's coronary attack according to etiology, whether it be due to (1) excessive work load (e.g., severely hypertensive), (2) inadequate input of energy (e.g., anemic, hypoxic, or diabetic), (3) a lowered degree of mechanical efficiency (e.g., in a severely adrenergic patient) or whether there is a combination of factors operative.

B. The presence or absence of congestive cardiac failure is noted.

C. The presence of absence of any cardiac arrhythmia is noted.

D. The possibility of hypovolemia is considered (this we find usually to be iatrogenic, e.g. those patients given diuretics and/or alpha blockers such as promazine).

E. It is noted whether there is any severe degree of adrenergic discharge exhibited by the patient (severe agitation, hypertension, tachycardia, and pallor).

Drug therapy

According to the features evaluated above we use the following drugs: isoproterenol, digoxin (inotropic drugs), methyl dopa (hypotensive agent), Cyclimorph and Wellconal (for analgesia and hypotension), Librium and Valium (for tranquilization), hydrocortisone (in the severely damaged heart), lignocaine and propranolol (in certain cases of arrhythmia).

An intravenous drip of 5 per cent dextrose/water is inserted as soon as the patient is admitted to the unit. A Hellige oscilloscope with pulsometer and alarm plus ECG writer is then connected to the patient for transthoracic recording as described above.

Isoproterenol therapy. This extremely valuable beta stimulator has 3 main effects: an inotropic effect, a peripheral dilator effect, and a chronotropic effect. Therefore it cannot be used in the presence of a tachycardia and should never be used without a continuously running oscilloscope.

We pay particular attention to the S-T displacement from minute to minute in the early phases of our therapy with isoproterenol. Any dosage which increases prevailing S-T displacement is contraindicated. It is found on this basis that the required drip rate for example may commence at 30 drops per minute, be 10 drops per minute after 1 hour, and thereafter 3 drops per minute. Concomitantly we have found a correlation between blood pressure and drip rate of isoproterenol and any excessive dosage at this stage raises the blood pressure. Furthermore we have found that a stage is reached (usually 3 to 5 days) when any further isoproterenol causes a deterioration and it is important to recognize (by ECG monitoring) the advent of this stage. Correlation between the level of blood pressure and the S-T segment displacement provides close tolerance to the drip rate.

Concentration of isoproterenol. In noncongestive cardiac failure cases we commence with four 0.2 mg. isoproterenol hydrochloride ampules per liter of 5 per cent dextrose/water. For patients with cardiac congestive failure we have commenced with 8 amps. per liter increasing in some cases to 16 amps. per liter before the balance between the efficacy of the drug and the additional fluid inflow is reached.

Digoxin therapy. We use this drug frequently in conjunction with isoproterenol. If the patient presents with sinus tachycardia or auricular fibrillation, we are able first to lower the pulse rate and so permit the infusion of isoproterenol. We administer 0.5 to 1 mg. of digoxin into the tubing of the drip under careful ECG surveillance. In the patient whose heart has been badly damaged with a falling R wave we have found that the timely administration of digoxin intravenously can restore the height of the R wave.

Methyldopa. This drug we administer orally in doses of 250 or 500 mg. and we do not hesitate to repeat the dosage every hour. We find this drug of particular value during convalescence, when it must be given at 8 hour intervals.

Propranolol. In many agitated adrenergic coronary patients we have found that isoproterenol may provoke numerous extrasystoles, and we have adopted the routine of giving this hypertensive agitated patient (with no evidence of CCF) one or two 10 mg. tablets of propranolol as soon as possible. We have found this type of patient to be extremely sensitive to minimal changes in his environment and it is for this reason that our unit consists of single-bed wards. Hypersensitivity to environment in this type of case bears a resemblance to that encountered in a case of tetanus.

We regard this medication with propranolol as pretherapy to be discontinued as soon as our hemodynamic principles can be adopted. The undesirable chronotropic effect of isoproterenol must not, however, be allowed to act immediately on the already alpha-activated myocardium of the adrenergic patient.

Fluid balance. The peripheral dilatation induced by isoproterenol may result in the

provoking of hypovolemia (low central venous pressure) and for this reason careful fluid balance charts must be kept on all patients. We have noticed that hypovolemia may precipitate (particularly in patients with badly damaged hearts) undesirable arrhythmias—e.g. flutter—which may easily be reversed by restoration of fluid balance. This aspect is of particular importance in diabetic coronary patients.

Steroid therapy. We add 200 mg. hydrocortisone per liter to the infusions of those patients exhibiting fever, S-T elevation or dipole reversal, and marked elevation of SGOT.

Lignocaine therapy. We have on occasion had recourse to therapy at the outset with this drug when a patient has presented with a supraventricular tachycardia.

Mobilization of patients

As soon as the S-T deviation reverts back to the isoelectric line, we gradually mobilize our patients. Those with dipole reversal are left longer in bed to obviate development of cardiac aneurysm. Patients on discharge are kept under fortnightly surveillance for the first 3 months.

Conclusions

It is obvious that until the etiology and natural history of any pathological process is clearly understood, effective therapy cannot be instituted. The large sums currently devoted to coronary research confirm that the etiology of the coronary attack has not as yet been satisfactorily evolved.

This paper presents our attempts at deduction from the laws of physics of the etiology of a coronary attack. In so doing we have shown that the finding of vascular occlusion by the pathologist in only a proportion of cases may have misdirected previous attempts at understanding the natural history of the attack.

The application of the principle of conservation of energy to the heart as a pump has enabled us to deduce factors capable of precipitating the coronary attack other than vascular occlusion. Of these, one apparently overlooked would seem to be the role of emotional stress in producing excessive noradrenaline secretion and hence a lowered index of mechanical efficiency of the myocardium. This lowered index of mechanical efficiency we have shown can lead to the coronary attack.

We have presented in considerable detail two cases (Cases A and B) in which the development of an infarct would appear to have been averted. According to our postulates, we attribute this to the timely adoption of corrective hemodynamic measures wherein the state of myocardial anaerobosis was rapidly converted to one of aerobosis. The same success has been achieved in 6 other similar cases. We thus postulate that an infarction is not the inevitable late sequel of the coronary attack.

We are unable for obvious reasons to conclude definitely that an infarction may precede thrombosis, although such a possibility must be considered in view of the findings of Kagan and associates[2] of a significantly higher incidence of early death in infarction not associated with occlusion.

With regard to therapy, we have shown that measures must be adopted whereby an aerobic energy balance is re-established. This may be achieved by reduction of the prevailing left ventricular pumping work and/or increase in the prevailing myocardial mechanical efficiency. The manner in which drug therapy is directed toward these ends has been detailed and illustrated in the 4 case reports.

We have shown reasons for the exclusive adoption of one transthoracic lead based on considerations of the Craib traveling dipole in assessing the status of the patient from an ECG point of view.

We have adopted these principles in 41 cases to date, with 3 cardiac deaths. 23 of these 41 patients were over 60 years of age and 11 were over 70 years of age.

We acknowledge our appreciation to Dr. J. C. Cawthorne, Superintendent of Addington Hospital, for permission to publish, to Dr. W. Botha, the Director of Hospital Services, Natal, for his enthusiastic encouragement, to Miss Thomson for photography, and Miss I. L. Powell for secretarial assistance. We would particularly record our gratitude to the nursing staff of the Cardio-Dynamic Unit, Addington Hospital.

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Experimental and laboratory reports

Ventricular dynamics in Bantu cardiomyopathy*

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The etiology of Bantu cardiomyopathy remains obscure. Macroscopically, the heart is enlarged in size, with increased wall thickness, cavity size, and weight. Light microscopy findings are entirely nonspecific, the outstanding features being variation in fiber size due to hypertrophy and atrophy of myocardial fibers, with variable degrees of edema, inflammatory cell infiltration, focal scarring, and endocardial fibrosis.[1-3] Furthermore, metabolic studies to date have failed to reveal any consistent defect, in particular evidence of defective oxidative metabolism. During routine left ventricular cineangiography performed in this group of patients, disturbance of ventricular wall motion was observed in every case and in some instances, local abnormalities appeared to be present. Abnormal patterns of contraction of the left ventricular wall due to localized areas of ischemia were recorded by Harrison[4] in kinetocardiograms of patients with coronary artery disease and termed "asynergy." This concept of impedence of myocardial performance from in-coordinate contraction as the morphologic basis of cardiac failure was subsequently further studied by others, notably Gorlin and associates[5] and Herman and co-workers, who established the technique of analysis of consecutive frames of the left ventriculogram for studying abnormalities in ventricular wall motion. In the absence of any other known etiologic factors, the possibility of defective ventricular dynamics being a significant contributory cause of the functional abnormality in Bantu cardiomyopathy was therefore considered. Accordingly, this study was designed to investigate ventricular wall motion and to define the type of abnormal spatial or temporal sequence of contraction.

Case material

Ten Bantu patients, between 16 and 55 years of age, were studied. Each patient presented with symptoms of severe left-sided heart failure, with or without right heart failure, of one month to one year in duration. Cardiomegaly, sinus rhythm, pulsus alternans (5 patients), left ventricular hypertrophy, loud third heart

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sound and Grade 2 apical pansystolic murmur of mitral regurgitation (4 patients) were present. The chest x-ray revealed cardiomegaly with congested lung fields, and the electrocardiogram (ECG) uniformly showed nonspecific changes of left ventricular damage. No patient had signs of valvular or pericardial disease as far as could be established none of the known causes of cardiomyopathy such as metabolic disorder or excessive alcohol intake were present.

Methods

Left ventricular cineangiography was performed in the 30 degree right anterior oblique projection by pressure injection of 30 to 50 ml. of 76 per cent Urographin directly into the left ventricle through a multiholed catheter which was passed retrogradely across the aortic valve. Cine angiograms were performed at 60 frames per second an ECG-activated flag indicator in the x ray field indicating the onset of systole. A synchronous ECG was recorded during the injection. The films were analyzed on a 35 mm projector (Tage Arno) only those of good quality contrast being accepted and the cycle with the clearest definition selected. Visual observation of several consecutive cardiac cycles in each film indicated that the regional contribution to movement remained entirely constant for each heart beat so allowing analysis to be confined to a single cycle. Reference was made to the concurrent ECG to exclude premature systoles which produce bizarre irregular contractions and postextrasystolic beats. Similarly no patient with bundle branch block was included. Some degree of mitral regurgitation is an almost invariable accompaniment in this disorder and was not a reason for exclusion from the study.

The ventricular outline in each consecutive frame for a complete cardiac cycle was drawn the papillary muscle bundles projecting into the lumen being ignored so that the outline encompassed all opacified areas. Two-dimensional measurements in this single plane were then made as follows (Fig 1). A line joining the cardiac apex L, and the midpoint of the aortic valve L was taken as the longitudinal axis L L this line was divided into four

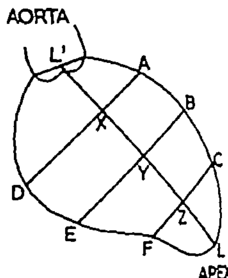


Fig 1 Nomenclature of measurements. The outline represents the inner ventricular wall as drawn from single frames of the dye-filled left ventricle. Length *L L* in centimeters is drawn from the midpoint of the aortic valve *L* to the apex *L*. *L L* is divided into 4 equal lengths by points *X Y* and *Z*. Hemiaxes are drawn at right angles through these points to the edge of the cardiac silhouette and labelled *AX BY CZ DX EY* and *FZ*.

equal lengths so producing points X, Y and Z. Hemiaxes were then drawn at right angles from these points to the edge of the cardiac silhouette. These hemiaxes, AX, BY CZ DX EY and FZ together with the length L L were reduced to life-size dimensions by obtaining the ratio of [illegible] ventricular catheter diameter to actual catheter diameter and modifying all measurements accordingly. Graphs were then plotted of the changes in these parameters with time during a complete cardiac cycle. In addition end-diastolic and end-systolic silhouettes were superimposed upon one another to produce a composite diagram of the range of ventricular wall movement during systole. An identical technique of analysis was applied to the cineventriculograms of 4 patients with normal ventricular function to provide comparison with normal ventricular dynamics.

Classification of ventricular wall movement

The term "asynergy" was used in [illegible] son as a general term to denote [illegible]

Table I. Classification of ventricular wall movement

Synergy—equal spatial and temporal sequence of contraction
- Normal
- Hyperkinesis
- Hypokinesis

Asynergy—local abnormality of contraction
- Akinesis: total lack of movement
- Asyneresis: local inadequate movement
- Dyskinesis: local expansile movement
- Asynchrony: temporal distortion of movement

ration of normal ventricular synergy detected by kinetocardiography. He described atrioventricular and intraventricular asynergy, so introducing the concept of disordered spatial and temporal sequence of contraction between different chambers of the heart, and within the same ventricle. In an analysis of the functional effects produced by ventricular aneurysm on myocardial performance, Gorlin and associates[6] used the term asynergy to embrace all disorders of ventricular wall motion, and classified these abnormalities as dyskinesis, akinesis, asynchrony, and asyneresis. Herman and co-workers[6] subsequently emphasized particularly that these defects are local abnormalities, confined to a single zone of the ventricular wall. In this study it has been found necessary to expand this classification in order to encompass all the abnormal types of ventricular wall movement encountered.

Abnormal movements fall into two distinct groups (Table I): synergic and asynergic movement. Synergic movement as exemplified by the normal heart implies synchronous uniform inward movement of all parts of the ventricular wall during systole with the reverse movement in diastole. In diseased ventricles, this synergic movement may be either increased or decreased in extent, so producing hyperkinesis, as in idiopathic hypertrophic subaortic stenosis,[7] or hypokinesis. The essential feature of this type of abnormality is that it involves all parts of the ventricular wall to an equal extent both in time and space. The basis of asynergy is fragmentation in the range or timing of movement between adjacent zones within the same ventricle. These terms are used in an entirely descriptive manner and alone provide no indication of pathologic cause nor specific functional consequence upon ventricular performance.

Results

Normal pattern of ventricular wall movement (Figs. 2, A and 3). The four patients with normal left ventricular function all exhibited an identical pattern of ventricular wall movement, consisting of the synchronous inward movement of all parts of the inner ventricular wall during systole with the reverse movement in diastole. Particular note should be made of the change in total length. In the normal heart, this mainly represents an obliteration of the cavity of the apex from apposition of the inward moving periapical ventricular walls, with a lesser contribution from contraction of the spiral fibers encircling the apex. This twofold effect explains the apparent increased rate of movement at the apex shown graphically.

Findings in Bantu cardiomyopathy

Hemodynamic findings and heart size in the 10 patients with cardiomyopathy are summarized in Table II. All patients showed increased end-systolic and end-diastolic volumes, with the residual fraction (LVESV/LVEDV) varying from 0.56 to 0.91 (normal 0.4 to 0.5). In 9 of the 10 patients, the left ventricular end-diastolic pressure was elevated, ranging from 21 to 40 mm. Hg. One patient had a normal LVEDP of 12 mm. Hg before angiography which rose to 20 mm. Hg after injection, with alternans.

Abnormalities of ventricular wall movement

1. HYPOKINESIS (FIGS. 2, B AND 4). All 10 patients showed diminished excursion of ventricular wall movement throughout the cardiac cycle. In general, this hypokinesis involved all areas of a given ventricle to an approximately equal degree. Compared with the normal graph, the parameter showing the greatest limitation of movement is the length from apex to aortic valve. This is primarily due to the restricted inward excursion of the ventricular walls adjoining the apex, which fail to become approximated during sys-

SHORTENING IN SYSTOLE → CMS

Panel A: Label	Values	Panel B: Label	Values	Panel C: Label	Values
BY		BY	3 0 / 4 0	AX	3 4 / 2 8
AX	4 8 / 3 5	AX	4·4 / 4 0	BY	3 2 / 2 8
CZ	4 0 / 3 5	CZ	3 6 / 3 2	CZ	2 3 / 1 8
DX	6 0 / 5 0 / 4 0	DX	6 8 / 6 2	DX	4 8 / 4 2
EY		EY	5 4 / 5 0	EY	4 0 / 3 4
FZ	3 0 / 2 5	FZ	3 2 / 4 8	FZ	2 6 / 2 2
L L	14 0 / 13 0 / 12 0	L' L	14 0 / 13·4	L L	9 6 / 9 0

A: SYSTOLE, DIASTOLE; 0, 83, 166, 249; TIME-MILLISECS

B: SYSTOLE; 0, 83, 166; TIME-MILLISECS

C: SYSTOLE; 0, 83, 166; TIME-MILLISECS

Fig 2 A B and C C phs of hemiaxes AX BY CZ DX FY and FZ and length LL in centimeter (ordinate) plotted against time in milliseconds (abscissa) through systole and ... side One ... equals ... Normal heart uniform symmetrical inward and outward movement of all hemiaxes ... movement of LL due ... of spiral fibers encircling the apex B Hypokinesis diminished range of movement affecting all parameters C Akinesis ... lack of movement of ... anterior ventricular wall

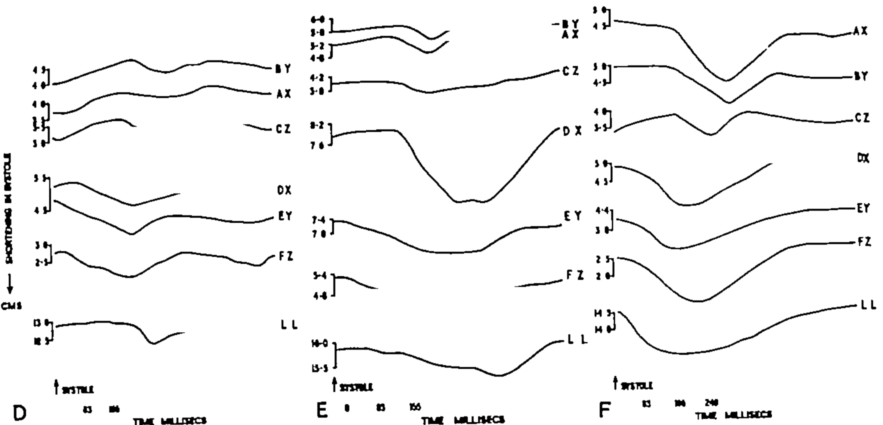


Fig. 2 D, E, and F Graphs of hemiaxes AX, BY, CZ, DX, EY and FZ, and length LL in centimeters (ordinate) plotted against time in milliseconds (abscissa) through systole and diastole. One frame equals 16.6 msec. D Dyskinesis: outward movement in systole of the anterior ventricular wall, AX, BY. E, Asynergy: normal movement of posterior basal wall DX with hypokinesis elsewhere. F Asynchrony: inward movement commences in posterior basal wall, DX and is followed sequentially by inward movement at the apex and finally anterior ventricular wall, AX. QRS duration and configuration normal.

Table II Hemodynamic findings and heart size in 10 patients with Bantu cardiomyopathy

Case no	*Heart rate (during angiography)*	*Cardiac index (L./min./M.²)*	*Systemic pressure (mm. Hg)*	*LVDP* (mm Hg)*	*LVESV/LVEDV†*
1	79	1 0	105/ 80	15–28	0 75
2	150	2 2	132/100	35–48	0 77
3	78	2 57	155/105	10–21	0 67
4	83	3 2	120/ 80	4–12	0 67
5	84	1 4	120/ 90	13–21	0 41
6	125	1 04	160/125	30–33	0 91
7	83	1	145/ 85	28–40	0 [illegible]
8	102	2 5	142/106	27 34	0 81
9	120	2 7	136/ 90	14–30	0 65
10	90	2 85	130/ 70	15–25	0 79

*LVDP Left ventricular diastolic pressure.

† LVESV/LVEDV Ratio of left ventricular end-systolic volume to left ventricular end-diastolic volume.

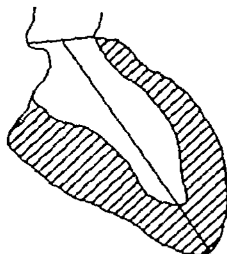


Fig. 3 The normal heart superimposed end-diastolic and end-systolic silhouettes. The cross-hatched area represents the range of movement inward from the beginning to the end of systole.

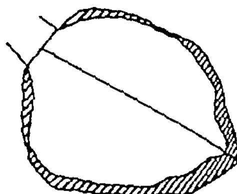


Fig. 4 Hypokinesis: uniform diminished range of movement involving the entire ventricular circumference.

tole so imparting a characteristic globular appearance to the end-systolic silhouette. Superimposed end-systolic and end-diastolic outlines indicate this diminished range of movement, and form a striking contrast with normal

2 All four types of *asynergy* were also found

AKINESIS (FIGS 2 *C* AND 5) or total lack of part of the ventricular wall was present in 3 ventricles, and was confined to those showing the most severe degree of restricted movement generally thereby representing the local extreme form of hypokinesis. The anterior and periapical areas were the areas of ventricular wall involved.

DYSKINESIS (FIGS. 2 *D* AND 6) or paradoxical outward movement in systole was present in 2 ventricles but was localized and not of severe degree. In each instance the dyskinetic zone was the anterior basal segment of the ventricle.

ASYNERESIS (FIGS. 2 *E*, AND 7) local diminished movement was present in ... ventricle The posterior basal segment ... the region of the mitral valve showed a range of movement approaching normal while the anterior and periapical area

Table III *Distribution of abnormalities of ventricular wall movement in 10 patients with Bantu cardiomyopathy*

Case no.	Hypokinesis	Dyskinesis	Akinesis	Asyneresis	Asynchrony
1	+	−	−	−	−
2	+	+	−	−	+
3	+	+	−	−	−
4	+	−	−	−	−
5	+	−	−	−	−
6	+	−	+	−	−
7	+	−	+	+	−
8	+	−	+	−	−
9	+	−	−	−	−
10	+	−	−	−	−
Total	10	2	3	1	1

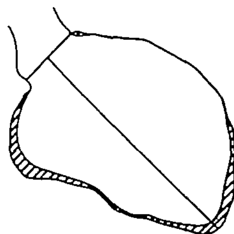


Fig. 5 Akinesis total lack of movement of the anterior wall of the ventricle.

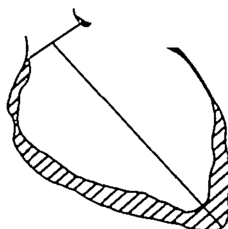


Fig. 6 Dyskinesis outward movement during systole of the anterior wall of the ventricle represented by the solid black area.

were severely restricted in the range of movement.

ASYNCHRONY (FIGS 2 *F* AND 8) or altered temporal sequence of contraction, was encountered in only one ventricle. Inward movement commenced at the mitral valve area, and was sequentially followed by inward movement of the apical regions and finally the anterior basal segment. This type of temporal dissociation of ventricular movement would suggest an abnormal source and direction of electrical excitation, but the con-current electrocardiogram showed sinus rhythm with normal QRS duration.

Table III summarizes the type and distribution of abnormal ventricular movements in the 10 patients studied.

Discussion

It is recognized that there are certain limitations inherent in this method of analysis of ventricular wall movement. Sudden pressure injection of a volume of hypertonic contrast material into the left ventricle may both depress contractility or preload parts of the ventricular wall irregularly so altering the visualized dynamic pattern of contraction. This effect may have greater significance in the myopathic failing ventricle than the normal

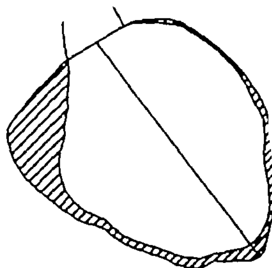


Fig 7 Asynergis normal range of movement in the posterior basal segment of the entricle, with diminished movement elsewhere.

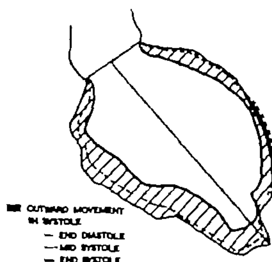


Fig 8 Asynchrony disordered temporal sequence of contraction result in general hypokinesis.

heart. In addition analysis in this study is made in a single plane so that abnormalities of a patchy nature throughout the three-dimensional left ventricular chamber may escape detection The major point of reference from which the length and hemiaxes are drawn namely the midpoint of the aortic valve does not bear a constant relationship to identical points on the cardiac silhouette throughout the cardiac cycle owing to the changing length and some degree of rotation of the heart within the pericardium Despite these technical limitations, Greene and associates[3] used similar measurements of the left ventricular silhouette in the right anterior oblique view to calculate left ventricular volume and obtained reproducible results.

In the normal heart, ejection of blood from the ventricle is accomplished by the synchronous inward movement of all points along the inner ventricular wall, with the reverse movement in diastole. This synergic action is dependent on two main factors (1) the rapid spread of electrical impulses to all fractions of the myocardium via the normal conducting pathways and (2) the ability of the excited muscle bundles to contract effectively and in unison Thus excitation spreading from an ectopic focus within the ventricular myocardium results in altered patterns of wall movement due to the abnormal direction and slower random fashion of excitation All patients studied in this series were in sinus rhythm with normal QRS duration so that aberrant excitation can be excluded as a cause of the abnormal contraction

Defective ventricular wall movement has also been shown to occur secondary to coronary arterial occlusion Tennant and Wiggers[9] demonstrated using myographic tracings, that local impairment of function of the myocardium resulting from an occluded vessel detrimentally affects the mechanical efficiency of the ventricle With the advent of cineventriculography abnormal movement has been shown to occur associated with thin fibrous scars in the form of ventricular aneurysms, or with normal muscle fibers interspersed with replacement fibrosis on an uneven basis. Correlative studies by Herman and associates[6] in patients with significant coronary artery stenoses have shown that zones of asynergy are directly related to the sites of the coronary artery lesions and are accompanied by equivalent and abnormalities in lactate metabolism However significant coronary artery pathology either focal occlusive atherosclerosis or the more specific type of arteritis associated with Friedreich's ataxia and related hereditary cardiomyopathies,[16] has been found absent in Bantu cardiomyopathy

In addition measurements of the coronary blood flow and myocardial oxidative metabolism in this disorder fall within normal limits, thus excluding the defective supply of oxygen to the myocardium as a cause of the altered dynamics.

It was postulated at the beginning of this study that movement in different areas of the myocardium might be normal but that dissociation in the spatial or temporal sequence of contraction between these zones might be present. This would result in ineffectual contraction of the ventricle as a whole. Thus, patchy fibrosis of the endocardium revealed by autopsy studies might be responsible for splinting localized areas of the endocardial wall so producing asynergy. The results of this study show however that the major defect in ventricular dynamics, present in every instance is diminished synergic movement rather than asynergy. Five of the ten patients did exhibit asynergy but the extent of these local abnormalities was minor compared with the severe degree of generalized hypokinesis uniformly found. However it cannot be inferred that such a splinting mechanism is not operative between individual muscle fibers with the technique of analysis used in this study. This only allows for comparison of movement between relatively large areas of the ventricular wall, no more subtle than can be detected by the naked eye. Indeed such a restricting mechanism between individual myofibrils would be expected to produce hypokinesis rather than asynergy provided that the restriction was uniformly dispersed throughout the ventricular muscle mass. Although focal areas of fibrosis are frequently present in the myocardium these are relatively sparse randomly distributed microscopic lesions, unlikely to cause such a profound dynamic disturbance of movement. In a detailed macroscopic and histologic study of 80 patients with cardiomyopathy Higginson and associates[2] described focal fibrous scarring of the endocardium in 48 an incidence of 60 per cent due to organization of thrombi on the endocardial surface of the ventricle. In the present smaller series, asynergy was present in 50 per cent of patients, and it is possible that this type of dynamic disturbance may be associated with these fibrous plaques superimposed upon the major abnormality of severe hypokinesis.

Conclusion

Ten patients with Bantu cardiomyopathy were investigated to assess the type of abnormal ventricular dynamics present. Hypokinesis was uniformly found with minor degrees of all types of asynergy in 50 per cent of patients. Asynergy per se cannot therefore be invoked as the major contributory cause of the severe functional abnormality in this disease.

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A comparison of the hemodynamic effects of ventricular and sequential A V pacing in patients with heart block

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At the present time, chronic symptomatic atrioventricular (A V) block is usually treated by permanent ventricular pacing Such treatment can prevent the recurrence of Stokes-Adams attacks, and also improve heart failure excessive fatigability and giddiness which may result from an abnormally low cardiac output. However ventricular pacing does not correct the temporal relationship between atrial and ventricular depolarization consequently only a proportion of atrial contractions occur at an appropriate interval before a subsequent ventricular systole and the advantages of coordinated A V activity are not restored

Normal A V relationships may be temporarily restored by employing a double electrode system and applying stimuli to pace both an atrium and a ventricle sequentially the P R interval can be regulated by controlling the delay between the two stimuli using a suitably designed external pacemaker unit. In the present investigation this technique has been used to determine individually the optimal P R relationships in a group of patients studied before the implantation of permanent ventricular pacemakers and thus to compare the hemodynamic effects of sequential A-V pacing at the most favorable P R interval with those of ventricular pacing alone. A second method of restoring normal A-V relationships in heart block is by synchronous pacing in which the spontaneous atrial depolarization (P wave) is used to trigger a ventricular pacemaker after a preset delay The P R interval can be varied but the subject's own sinus activity determines heart rate. It is, therefore, more appropriate than sequential pacing for the long term treatment of patients with chronic A V block but less suitable for a hemodynamic investigation in which spontaneous rate changes are better avoided The results of the present study which

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indicate the effects of optimally timed atrial systole, are applicable to both techniques. A brief preliminary report based on some of these experiments has been published.[1]

Patients and methods

Studies were performed on ten patients, eight men and two women whose ages ranged between 58 and 83 years (mean 71). All had had symptoms from second or third degree A V block with the exception of one in whom the indication for permanent pacing was recurrent sinus bradycardia. At the time of the investigation five patients had complete A V block, one had second degree A-V block, two had first degree A V block, and two had normal conduction. Both patients with normal conduction developed first degree A V block during atrial pacing. Seven of the ten patients had evidence of myocardial disease. One of these had a history of myocardial infarction and three others had electrocardiographic changes suggestive of ischemia. In five instances, chest x-rays showed cardiomegaly (cardiothoracic ratio 53 to 63 per cent).

Measurements were made at the time of routine insertion of a temporary pervenous ventricular pacemaker usually two days before the permanent unit was implanted. The investigatory nature of the subsequent hemodynamic measurements was explained to the patients, and all agreed to cooperate. An additional bipolar pacing electrode* was positioned with the tip near the lateral wall of the right atrium to permit atrial pacing, the left radial artery was cannulated and a polyethylene catheter (1 mm in internal diameter) was passed to the low superior vena cava. The bipolar electrodes were connected to a Medtronic† coupled pulse generator (Model 5837) which could be set either for ventricular pacing or for sequential A V pacing at variable heart rates and P R intervals.

Systemic arterial pressure was measured from the left radial artery and central venous pressure through the polyethylene catheter using Statham P23Db transducers connected to a direct writing Sanborn recorder. Cardiac output measurements were made by a dye dilution technique using 1 ml. injections (7 mg.) of indocyanine dye into the superior vena cava with 5 ml saline flushes, sampling through a Gilford densitometer from the radial artery using a Harvard constant speed pump at 30 ml. per minute. After each output measurement, blood was reinfused into the artery. Dye curves were recorded directly and the output signal was also passed to a Lexington analogue computer which provided an integration curve on the recorder for subsequent output determination. The computer was calibrated with a 1 : 1,000 dilution of dye in blood prepared with a Hamilton micropipette.

Observations were made during ventricular pacing and during sequential A V pacing with P R intervals of 50, 100, 150, and 200 msec. At least two minutes were allowed between changes of pacing mode to enable the output and pressures to stabilize.

Heart rate was set at 10 beats per minute above the sinus rate (sinus rate +10) in order to obtain atrial capture. Additional measurements were made in six patients at 40 beats per minute faster than the sinus rate (sinus rate +40).

In one patient, cardiac output measurements during A V pacing were made only with P R intervals of 100 and 150 msec., and in another patient a variable stimulus-depolarization delay precluded measurements at fixed P R intervals. In seven of the ten patients central venous pressure tracings showed satisfactory wave forms at all P R intervals; in three cases some curves were damped and were therefore discarded.

The statistical significance of the results was tested by the t test for paired comparisons.

Results

The effects upon cardiac output

SINUS RATE +10 (80 TO 100 BEATS PER MINUTE). Output measurements were available for both ventricular pacing and for A V pacing at the full range of P R intervals in eight patients. The results for the group are shown in Fig. 1. Sequential A V pacing with a P R interval of 50 msec. did not result in significantly higher outputs than were obtained with ventricular pacing alone. In

*Bill C-3 bipolar electrode, U.S. Catheter and Instrument Co., Glens Falls, N. Y.
†Medtronic, Inc., Minneapolis, Minn.

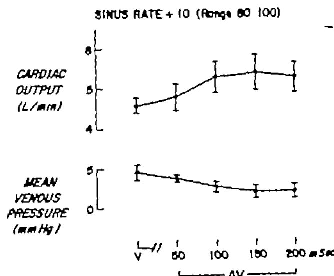


Fig 1 The mean cardiac outputs of eight patients and the mean central venous pressures of seven patients during ventricular (*V*) pacing and during sequential atrioventricular (*AV*) pacing at 10 beats per minute above sinus rate with P R intervals of 50 100 150 and 200 msec. Each vertical bar represents two standard errors of the mean.

Table I Cardiac outputs during sequential A V pacing at 10 beats per minute above sinus rate with P R intervals of 100 150 and 200 msec

Patient N	Cardiac output (L./min)		
	100 msec	150 msec	200 msec.
2	4 8	4 7	4 5
3	4 5	4 5	4 8
4	3 9	4 0	3 9
5	6 3	5 6	5 9
6	5 2	5 3	5 7
8	6 5	7 2	6 3
9	7 1	7 5	6 9
10	4 1	4 6	4 0

contrast the outputs were significantly higher ($p < 0.02$) at each of the other three intervals Although the outputs averaged for the group showed little difference from 100 to 200 msec. there were marked individual variations within this range with increments of up to 0 7 L. per minute (Table I) The highest output was obtained with a P R interval of 150 msec. in four cases, 100 msec in two cases, and 200 msec in two cases.

When ventricular pacing was compared with sequential A V pacing at the individually determined optimal P R interval for all the ten patients who were studied, the cardiac output increased 24 per cent, from 4 6 ± S.E.M 0.4 L. per minute to 5 7 ± 0 4 L. per minute (Fig 2) The difference is highly significant ($p < 0.001$).

SINUS RATE +40 (110 TO 125 BEATS PER MINUTE) Measurements were made in six patients, and the P R intervals could be varied systematically in five. The highest cardiac output was obtained with a P R of 200 msec. in one of these cases, and 150 msec. in the remaining four A comparison of the mean cardiac outputs during ventricular pacing and during sequential A-V pacing at the optimal P R interval for the six patients studied at the faster rate showed an increase of 25 per cent from 4 9 ± 1.0 L. per minute to 6.1 ± 1.3 L. per minute. This difference is highly significant ($p <$ 0 001) The augmentation obtained at the two heart rates in the same six subjects was similar (Fig 3)

The effects upon blood pressure Ventricular pacing resulted in a phasic variation of arterial pressure depending upon the changing relationship of atrial and ventricular activity the systolic and diastolic pressures were therefore taken to be the

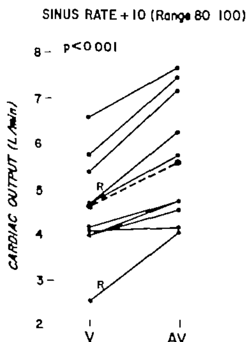


Fig 2. Cardiac outputs of ten patients during ventricular (V) pacing and during trioventricular (AV) pacing t 10 beats per min t bove sinus rate ith the individually determined optimal P R interval. R indicates retrograde conduction, seen in tw cases during ventricular pacing The mea ugmentation produced by AV pacing (broken line) is 24 per cent.

mean of the values obtained during the phasic variation. Sequential A V pacing *always stabilized the pressure. At the sinus* rate +10 the systolic pressure was higher during optimal A V pacing than during ventricular pacing in seven patients, showed no change in two patients and was lower in one. However the mean increase in systolic pressure was small (from 163 to 170 mm Hg) and not statistically significant (Fig 4) At sinus rate +40 the five patients from whom systolic pressures were avail able all showed augmentation. During ventricular pacing the average systolic pressure for the group was 158 ± S.E M 9 mm Hg and during optimal A V pacing the average pressure was 176 ±9 mm Hg ($p < 0.02$)

Diastolic pressures showed little change at either heart rate

The effects upon central venous pressure In seven patients, central venous pressure measurements were available at sinus rate +10 for both ventricular pacing and for A V pacing at the full range of P R ntervals. The results for the group are shown in Fig 1 When ventricular pacing was compared with sequential A V pacing at the P R ntervals which gave the highest individual cardiac outputs, the venous pressure decreased from 5.5 ± S E M 1 0 mm Hg to 2 5 ±0 5 mm. Hg ($p < 0.01$ Fig 4)

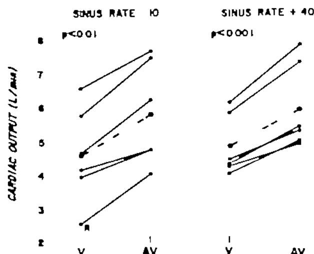


Fig 3 Cardiac outputs in six patients paced initially t 10 beats per minut above sinus rate, hen 40 bea per minute abov sinus rate. The symbols are the same as in Fig 2 The augmentation of output with AV pacing is similar at both rates.

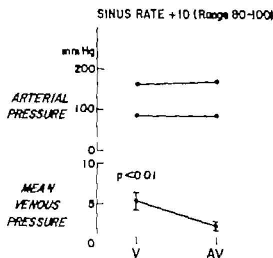


Fig 4 Mean systolic diastolic, and central venous pressures in ten patients paced at 10 beats per minute above sinus rate A V pacing produced a significant fall in venous pressure but essentially no change in arterial pressure.

At sinus rate +40 central venous pressure measurements were obtained in six patients in five of whom the P R intervals could be varied systematically In these five cases the lowest pressure was obtained at an interval of 150 msec. The average venous pressure during ventricular pacing was 3 9 ±1 1 mm Hg and during A V pacing at the optimal P R interval it was 1 7 ±0 6 mm Hg ($p < 0.05$)

Discussion

Properly timed atrial systole increases ventricular volume at end diastole, and augments stroke volume by the Starling mechanism.[2] Conversely an atrial contraction occurring inappropriately during ventricular systole may hinder ventricular filling by causing retrograde flow into the veins, and may also interfere with normal A V closure permitting valve regurgitation. This results in decreased stroke volume and raised venous pressure.

In A V block, the atria and the ventricles beat independently and at different rates. This causes a phasic shift in the A V relationship and results in a beat to-beat variation in stroke output. The variation is reflected in changing heights of the arterial pressure waves and changing pulse pressures. Similar phasic pressure changes occur during ventricular pacing with dissociated atrial activity (Fig 5)

Analyses of changes in pressure tracings recorded during ventricular pacing have been used by others both to evaluate the hemodynamic contribution of atrial systole and also to determine the optimal P-R interval in man. Thus Kroetz and associates[3] used beat to-beat changes in pressure gradients in patients with aortic stenosis to estimate that atrial contraction augmented stroke volume by an average of 27 per cent Ruskin and co-workers[4] employed a technique of pressure wave analysis to calculate that the increase could be as much as 400 per cent in patients without valve stenosis paced at fast rates. Information on the optimal timing of atrial contraction based upon beat to-beat changes in arterial pressure was obtained by Carleton and associates[5] who showed that during ventricular pacing the most effective P-R interval depended upon heart rate.

Such methods are necessarily indirect. Furthermore, they may not reliably indicate the optimal timing of atrial systole or the degree of augmentation which can be obtained under steady-state conditions. In particular several consecutive inappropriately timed atrial contractions may limit ventricular filling and exaggerate the effect of the first contraction occurring within the physiologic range.

Studies on the effects of atrial contraction under steady state conditions have not previously been directed at the problem of optimal A V relationships. Atrial pacing is known to result in higher cardiac outputs than ventricular pacing at the same rate,[6] but the P R interval cannot be controlled, and the method is inapplicable to patients with A V block. Very few studies have been reported which compare the hemodynamic effects of A V pacing with the effects of ventricular pacing in patients with A V block. Samet and associates[7] showed that cardiac output in six patients was augmented by an average of 10 per cent under these circumstances. In five of them the P R interval was arbitrarily set at 1[illegible] msec. but in the sixth patient the augmentation increased from 16 per cent to 33 per cent when the P R interval was increased to 180 msec The overall difference between these results and those of the present study

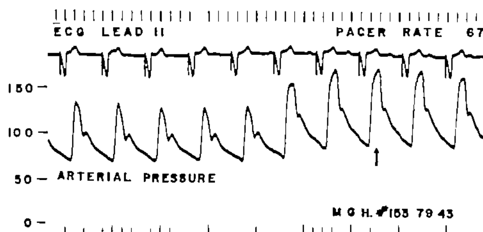


Fig 5 Radial artery pressure from patient with complete A-V block during fixed-rate ventricular pacing The peak systolic pressure is seen when the P R interval is 270 msec (arrow).

are likely to have been due in part to the individual determinations of the optimal A V relationships in our patients.

Results may also be influenced by the time at which measurements are made after a change in pacing mode. We chose an interval of approximately 2 to 4 minutes which is sufficiently long for a relatively steady state to have been achieved [9] However we do not have data to show that augmentation resulting from an appropriate P R relationship would persist. In some instances, particularly in patients who had normal flows during ventricular pacing cardiac output might have returned toward control values if observations had been made serially over a long period. This regression would be mediated by a partial withdrawal of sympathetic activity Evidence for a similar regulatory mechanism in the peripheral vascular system was found in the arterial pressure tracings which usually showed a marked increase immediately after a more favorable P R interval was initiated followed by a slow fall toward control levels. But, any reduction in sympathetic activity implies that the heart is encroaching less on one of its principal reserve mechanisms. The demonstration of even a transient improvement in hemodynamic measurements with an alteration of pacing mode may therefore be of long term significance.

Although alterations in pacing mode at the slower heart rates affected arterial pressure only transiently the instantaneous changes usually had a predictive value in that a brief increment occurred when a more favorable P R interval was initiated Falls in venous pressure which occurred during pacing at a favorable P R interval tended to persist until the mode was changed. Thus, significant changes in venous pressure were found as a result of A V pacing whereas no significant changes were noted in arterial pressure (Fig 4)

Cardiac output during ventricular pacing was similar at the slower and at the faster heart rates in five of the six patients for whom comparative data is available This is a common response for patients with A V block as well as for normal subjects in whom heart rate is varied by atrial pacing [11] The average augmentation for the group in changing from ventricular to A V pacing was similar for the two heart rates but because of the need for atrial capture during sequential pacing we were not able to study patients at slower heart rates at which time the atrial contribution may be less important.

The study confirms the value of properly timed atrial systole to the performance of the heart in patients with chronic A V block. Many patients with chronic heart block do not have serious myocardial disease and the functional reserve of the cardiovascular system in these cases is such that ventricular pacing is satisfactory treatment. However in patients with poor

myocardial function or low cardiac outputs, the value of the atrial contribution provided by sequential or synchronous pacing may be of critical importance.

Summary

A comparison was made of the effects of ventricular pacing and sequential A V pacing at individually determined optimal P R intervals in ten patients with A V block. At heart rates 10 beats per minute faster than sinus rate the average cardiac output increased from 4 6 to 5 7 L. per minute (24 per cent $p < 0.001$) and central venous pressure fell from 5 5 to ? 5 mm Hg ($p < 0.01$) with the restoration of properly timed atrial systole. The results were similar in six of the patients studied at a rate of 40 beats per minute faster than sinus rate.

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Continuous radioelectrocardiographic monitoring of football and basketball coaches during games

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With the development of electrocardiographic monitoring systems for patients critically ill in the postoperative state, after serious injury, or with cardiac disease there has been an increasing interest in monitoring individuals in more normal environments and during the stress of their normal activities. The improved outlook for patients with myocardial infarctions during the past few years has been attributable to a great extent to the development of coronary care units where patients can be constantly monitored during the first few critical postinfarction days. At times, the monitoring of an individual who presents with symptoms suggestive of a cardiac arrhythmia and a normal cardiac mechanism can clarify an otherwise puzzling disorder. Bellet and others[1-4] have described the response to physical stress in individuals monitored while riding a stationary bicycle; others have described disturbances in the cardiac mechanism in patients under emotional stress. Athletes have been examined by electrocardiography immediately after the stress of athletic events. There has been no report on the effects of the stress of athletic events upon the heart action of coaches whose teams were in competition.

This study involved the continuous electrocardiographic monitoring of 30 football and basketball coaches, ages 24 to 56, throughout a period from 5 minutes before game time, during the entire game, and 5 minutes afterward with the half-time period excluded. Prior to monitoring, 28 of the coaches had a history taken; the physical examination included chest x-ray or cardiac fluoroscopy, a routine 12 lead electrocardiogram, a double Master's exercise test, complete blood count, urinalysis, urea nitrogen, fasting blood sugar, cholesterol, and total and fractional lipid determinations. Of those examined, one had sustained a myocardial infarction two years previously with subsequent infrequent anginal episodes. He had a normal resting electrocardiogram with a positive Master's exercise test. Another coach had a history of rheumatic fever and a Grade I-VI apical systolic murmur, but was

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asymptomatic. There was one hyperten sive subject in the group with a diastolic pressure of 90 mm. Hg The remainder had essentially normal physical findings and laboratory studies and were asymptomatic

Monitoring was performed with a radio-electrocardiograph RKG 100 produced by Telemedics Southampton Pa.[1] Elec trodes were placed at the level of the fifth ribs slightly anterior to the midaxillary lines after careful cleansing of the chest wall and connected to a battery powered FM transmitter The transmitter unit weighed 10 ounces and was 1 by 3 by 4½ inches in size and it broadcast on a single frequency allocated and approved by the Federal Communications Commission The receiver was attached by a special con nector to a standard electrocardiograph which recorded the signal on paper at a speed of 25 mm per second Receiving equipment was usually located near the subject but satisfactory signals were recorded through dressing room walls and up to a distance of several hundred feet. The major technical difficulty encountered with the monitoring equipment was associated with poor electrode contact.

Results

Our main interest in this study con cerned (1) the average heart rate at rest and its change during the period of stress (2) occurrence of ectopic beats or abnormal rhythms and (3) S-T T wave or QRS changes. The results are tabulated in Table I All coaches exhibited sinus ar rhythmia during the monitoring period which became less evident as the rate in-creased. Three had pregame heart rates less than 100 the others had rates ranging upward to 150 per minute After the be ginning of the game each coach rapidly reached a rate which was sustained with minor changes throughout the game period. A similar observation was made by Collins on racing car drivers.[2] Unlike Collins we did not observe a rapid decline of the tachycardia during the postgame period The maximum rate observed was 188 beats per minute in a coach who maintained an average rate of 166 throughout a game. The coach who had had a prior myocardial infarction occasionally showed frequent ventricular ectopic beats of multifocal origin (Fig 1 *A*) There was one short period of paroxysmal atrial tachycardia in a coach who did not have a premonitor ing work up (Fig 1 *B*) There were no significant S-T T wave, or QRS changes recorded None of the coaches developed symptoms during monitoring Major game events such as touchdowns, pass intercep tions, fumbles, missed baskets, or time-out periods were noted on the electrocardio-graphic paper as they occurred during the

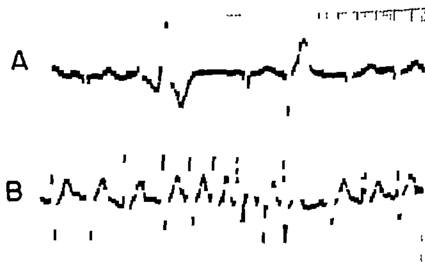


Fig 1 *A* Multifocal premature ventricular beats in a football coach with known coronary disease *B*, Short run of atrial tachycardia noted on another football coach.

Table I. Average heart rate and arrhythmias seen in coaches monitored continuously during football and basketball games

Subjects	No.	Average age	Average heart rates			Ventricular ectopic beats			Atrial ectopic beats		
			Resting	5 min. pregame	During game	Rare	6 or more per min	Multi-focal	Rare	6 or more per min	PAT*
Football coaches	18	34	70	109	132	4	1	1	9	0	1
Basketball coaches	12	32	68	113	132	4	1	0	2	1	0

*PAT: Paroxysmal atrial tachycardia.

progress of the games. There were no noticeable changes in heart rates with such events, and ectopic beats or other arrhythmias were not precipitated. Smoking during the game did not result in changes in average heart rate.

Discussion

The electrocardiogram has been studied extensively following physical stress both of a minor nature such as the Master's exercise test and after extreme physical effort including long distance running, skiing, strenuous marching, and other forms of sports.[8] Likewise, many studies describe the effects of psychic stress on the electrocardiogram. A recent report of stress produced by automobile driving reveals the fact that tachycardia of a driver and his passenger parallel each other during the stress situation of city driving. Emotional stress has been reported to precipitate a variety of disturbances in cardiac rhythms including atrial and ventricular ectopic beats and paroxysmal atrial fibrillation which subsided when the stress situation was corrected. Wheeler[8] mentioned that palpitations and tachycardia are among the most widely recognized effects of emotional stress although major arrhythmias may occur. T wave changes associated with emotional states are now a known fact. Stressful suggestions in apparently normal subjects under hypnosis resulted in tachycardia, T wave inversion, T wave elevation, and S-T depression. Changes in the basic heart rate have been shown to be a valuable indicator of psychologic and physical stress response and have been used as one of the parameters in monitoring aircraft and spacecraft pilots.

Bellet and associates[2] described the following as normal physiologic responses to exercise in a group of 135 normal individuals who were monitored while riding a stationary bicycle at 25 to 30 miles per hour for 3 minutes: sinus tachycardia (100 per cent of subjects), increased P wave amplitude (85 per cent of subjects), S-T depression of the junctional type 1 mm or more (75 per cent of subjects), diminished (68 per cent of subjects) or increased (9 per cent of subjects) T wave amplitude. He observed ventricular premature beats in only two subjects. The maximal heart rate for healthy children, aged 12 to 15 years, is 198 plus or minus 14; at age 30, healthy adults will have a maximal heart rate of 190 plus or minus 12; and at age 50, 174 plus or minus 12. At age 70, the maximum rate is 146 plus or minus 12.[4]

Apparently healthy football and basketball coaches develop and sustain a symptomless tachycardia during the stress of a game in which their team competes. Infrequent ventricular and atrial ectopic beats may occur but are unrelated to major events throughout the course of a game. Multiple focal premature ventricular beats occurred only in the one coach with known coronary disease during the stress of the game.

Summary

Thirty football and basketball coaches were monitored continuously with a radio-telemetric monitoring device throughout games in which their teams competed. All responded to the stress of the game with an increase in heart rate averaging 42 beats per minute over resting rates in the pregame period and with an additional increase of 21 beats per minute during the game period. Eight coaches developed rare premature ventricular beats and in two they were frequent. The only coach with known coronary disease had multifocal premature ventricular beats. Eleven developed rare premature atrial beats and in one they were frequent. A short run of atrial tachycardia occurred in one coach. None of them developed symptoms or significant S-T, T or QRS changes.

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Determination of left ventricular wall thickness by angiocardiography

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The accurate angiocardiographic determination of left ventricular wall thickness has become of great importance since recent conceptual advances have made the in vivo calculation of left ventricular muscle mass and wall stress and more importantly of derived measurements such as the force-velocity relationships[1] possible. Earlier experiences by several workers[2] indicated that during systole a 100 per cent increase of the thickness of the free lateral wall of the left ventricle photographed in posteroanterior direction was not uncommon. In many instances, this led to a striking increase in systolic left ventricular muscle mass when compared to the diastolic mass—a rather obvious absurdity. Furthermore, direct measurements of the left ventricular wall thickness (LVWt) throughout the cycle by caliper devices[3] and photographic measurement of implanted lead bead surface clips[4] in dogs indicated strongly that the increase in thickness of the active contractile wall elements from diastole to systole varied at most from 25 to 45 per cent.

In an effort to elucidate this discrepancy an analysis was carried out in 31 patients with congenital heart disease and different types of cardiac load and ventricular wall response. Wall thicknesses were measured directly from the PA film throughout one cycle and compared with those predicted from a calculation which included the assumption of a constant muscle mass (that measured in end-diastole when the left ventricle reaches the most symmetrical ellipsoid shape) and variable ventricular cavity size. In instances where the two measurements varied by more than 0.5 mm. the films were scrutinized for traces of embedded contrast material in an effort to see whether the correct measurement could have been made with the help of the computer predicted wall thickness.

Methods and materials

Biplane serial angiocardiographic films were studied in 31 patients randomly selected from a larger series with mostly congenital heart disease. Nine had aortic stenosis or coarctation of the aorta (AS); 3 of these were infants. One had aortic

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regurgitation (AR) and 3 mitral regurgitation (MR). Six patients had a ventricular septal defect (VSD), 1 an atrial septal defect (ASD), and 2 patent ductus arteriosus (PDA). Five had myocarditis of varying types and degrees of severity, while 3 patients had idiopathic hypertrophic subaortic stenosis (IHSS). One patient had no demonstrable heart disease. Their ages ranged from 4 weeks to 32 years. Only 4 of the patients were older than 16 years of age.

The angiocardiograms were recorded on serial film changers in posteroanterior and lateral directions at film speeds of 12 frames per second over an average of 2 cycles. From 8 to 24 films were available for analysis in a given patient. The films were then rearranged to form a composite extending over one cycle. The contrast medium was injected in the left ventricle in all but 1 patient. Instances where premature ventricular beats resulted from the injection were excluded from analysis. Other details of the procedure and of the methods of calculation of ventricular volume and left ventricular muscle mass and weight have been published earlier.[6,7]

Some variations in the data processing methods employing the Scientific Data System 940 Computer were inaugurated and will be described here. Unlike in previous studies, the timing of the exposure of the film was defined *in milliseconds by* measuring the interval elapsed since the onset of the q wave of the immediately preceding QRS complex in Lead II or III. The cavity was traced following the boundary formed by the dense contrast material inside the cavity and the inside edge of the radiolucent left ventricular muscle wall. The middle third of the total length of the free wall of the left ventricle was delineated by drawing the boundary between the outer edge of the ventricular wall and the still more radiolucent pericardium. Between 10 to 20 measurements were made of this segment and the average value was recorded. Left ventricular muscle mass was then calculated utilizing the wall thickness observed at the time of the largest volume prior to ventricular contraction (end-diastolic volume). In patients with heavy trabeculae carneae during the diastolic and early systolic phase of contraction, the inner boundary was smoothed by interpolation.

For each film analyzed, two separate volumes were computed. The first is the inner ventricular volume or "blood volume," derived from the general equation for the volume of an ellipsoid of revolution; this equation is a function of the two transverse (semi-minor) axes, b and c, and the longest (semi-major) axis, a, and can be expressed in the form

$$V = f(a, b, c). \qquad (1)$$

The second volume represents the total volume of the ventricle, and as such, it includes both the inner "blood" volume and the contribution made by the ventricular wall itself. The same equation is used, but each axis is increased in length by a distance that is equal to the wall thickness. Thus, the total volume takes the form

$$W = f(a + h, b + h, c + h). \qquad (2)$$

By differencing equations (2) and (1), a quantity U is determined that represents the contribution to the total volume that is made by the ventricular wall, that is,

$$U = W - V = f(a + h, b + h, c + h) - f(a, b, c) \qquad (3)$$

represents the ventricular muscle volume. The muscle weight was then directly calculated by multiplying the volume difference in equation (3) by the specific gravity of the myocardium, taken to be 1.05.

When equation (3) is solved at end-diastole, the volume U_{ed}, so determined, was considered to be the constant parameter representing the true ventricular muscle volume. Subsequently, for each film in the sequence of the cardiac cycle, equation (3) and the parameter U_{ed} were employed to calculate the corresponding values for the wall thicknesses. Thus, in general terms, the i^{th} wall thickness associated with the i^{th} film is calculated by solving for h_i the equation

$$U_{ed} = f(a_i + h_i, b_i + h_i, c_i + h_i) - f(a_i, b_i, c_i). \qquad (4)$$

This equation is, in fact, a third order (cubic) equation which is of the form

$$U_{ed} = \alpha h_i^3 + \beta h_i^2 + \gamma h_i \qquad (5)$$

where α, β and γ are constant coefficients in each frame representing sums of cross products of the three axes of the ellipsoid.

Since a general cubic equation does not readily lend itself to a straightforward analytic solution, a Newton-Raphson iteration technique was implemented into the program to solve equation (5) for the wall thickness, h_i. This is a numerical method for determining the real roots of an equation by successive approximations utilizing the first derivative. Since a cubic equation was to be solved, at least one real root was assured; furthermore, the value of the wall thickness as directly measured from each film served as a first estimate for the values of this real root.

In order to use this iterative technique in these studies, it was necessary to redefine equation (5) as a function g of the wall thickness, h; thus the analytic representation for determining the wall is

$$g(h) = \alpha h^3 + \beta h^2 + \gamma h - U_{vol} \qquad (6)$$

where U_{vol}, the ventricular muscle volume, is now the constant term in the general cubic equation. The first derivative with respect to h is immediately determined from equation (6) as the expression

$$g'(h) = dg(h)/dh = 3\alpha h^2 + 2\beta h + \gamma \qquad (7)$$

Using the analytic results of equations (6) and (7), the iterative equation for the Newton-Raphson technique has the form

$$h_{j+1} = h_j - [g(h_j)/g'(h_j)], j = 1, 2 \qquad (8)$$

where the subscripts, j, serve only as counting indices. Equation (8) is solved iteratively for each wall thickness in the sequence of films representing the cardiac cycle. The iteration was executed either ten times, as an arbitrary cutoff, or until $h_{j+1} - h_j < 0.005$; that is, until two successive iterations yielded no further significance in the third decimal place of the result. Since equation (8) converges quite fast, the magnitude criterion is the one which terminated the iterations in most instances. For the first iteration in equation (8), h is assigned the originally measured

Table I. Per cent difference between end-diastolic and end systolic wall thickness in 31 patients with congenital heart disease

Group I		*Group II (recognizable boundary)*		*Group III (no recognizable boundary)*	
Disorder	%	*Disorder*	%	*Disorder*	%
Aortic stenosis, endocardial fibroelastosis	36	Aortic stenosis	60	Aortic stenosis	60
Aortic regurgitation	42	Aortic stenosis	84	Aortic stenosis	96
Ventricular septal defect	64	Mitral regurgitation	92	Aortic stenosis (postop.)	72
Ventricular septal defect	47	Mitral regurgitation	92	Aortic stenosis (infant)	59
Idiopathic hypertrophic subaortic stenosis	42	Ventricular septal defect	70	Aortic stenosis (infant)	107
Endocardial fibroelastosis	15	Ventricular septal defect	64	Coarctation of the aorta	69
Myocarditis	50	Patent ductus arteriosus	89	Mitral regurgitation	107
Myocarditis	28	Idiopathic hypertrophic subaortic stenosis	52	Ventricular septal defect	44
Anomalous coronary artery	24	Atrial septal defect	65	Patent ductus arteriosus	72
Myocarditis	50	Normal	70	Idiopathic hypertrophic subaortic stenosis	77
				Ventricular septal defect	133
A (10 patients)	39.8%	A (10 patients)	73.8%	A (11 patients)	92.5%
(2.26 to 3.21* 0.40 to 0.60)†		(1.05 to 1.60 0.37 to 0.70)		(1.55 to 2.75 0.50 to 0.72)	

*Maximal actual increase in wall.
†Minimal actual increase in wall.

value of the wall thickness as determined from the end-diastolic film for the first approximation

Finally a comparison was made in each film between the computer predicted wall thickness and that measured directly Routine statistical analysis was applied to calculate the significance of the observed differences.

Results

Diastolic wall thickness, as measured directly varied from 0 30 cm in a patient with severe myocarditis (subsequently confirmed at autopsy) to 2 26 cm in a patient with severe IHSS This wide range of measurements reflected the variety of disorders included for this study (Table I) In each patient the wall thickness increased to its maximum value during end systole The measured values in systole varied from 15 per cent of the diastolic thickness in a patient with endocardial fibroelastosis, to 133 per cent in a patient with a ventricular septal defect.

Comparison of the predicted with the measured wall thickness showed that the observations fell into three distinct categories (Table I) In 10 patients, in the first group there was no significant difference (0 5 mm or less Fig 1) All of the patients with myocarditis and none of those with aortic stenosis (except for the infant with aortic stenosis and coexisting severe fibroelastosis) fell into this group. Conversely of 11 of the 31 patients in whom the computed wall thickness could not be seen in the films taken during the late phases of ventricular contraction, 6 had aortic stenosis or coarctation of the aorta with definite ventricular hypertrophy Left ventricular weights in this group were as high as 269 grams per square meter (Fig. 2) Furthermore in all but 2 of these 11 pa-

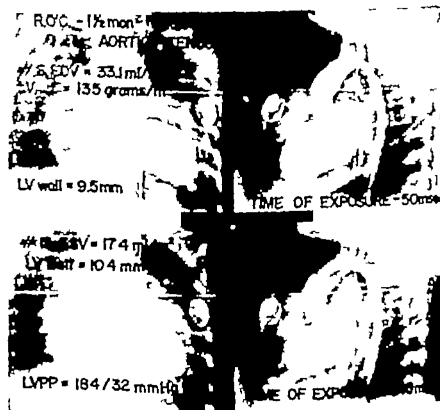


Fig 1 End-diastolic (upper) and late systolic (lower) films taken in anteroposterior and lateral direction of an infant with aortic stenosis and fibroelastosis. Exposure times are at 50 and 210 msec respectively after onset of contraction (heart rate 120 beats per minute). Note the smooth outline of both cavities with the ... of catheter tip against the inner boundary of the left ventricular wall. There ... 10 per cent thickening of the wall and complete agreement between predicted and measured wall thickness.

tients, the end-diastolic volume was normal or below normal the ejection fractions were normal definite hypertrophy was present, and adequate ventricular function with absence of cardiac dilatation was obvious. The two exceptions had AR and MR but showed no clear evidence of an abnormally functioning left ventricle

In the remaining one third of the 31 patients (10 individuals) careful re-exami nation of the films did reveal evidence of contrast material trapped within the tra beculae carneae (Figs. 3 and 4) These observations, and those in a patient in whom fortuitously the tapered tip of a No. 7 Eppendorf catheter remained in apposition to the free wall (Fig 3) indicate that in the majority of the patients (21 of 31) reliance on direct measurement of left ventricular wall thickness during late systole will lead to serious overestimation (Fig 5) In fact, even when the predicted wall thickness was demonstrated as a second fainter border of contrast the observation was not accepted by several trained radiologists until these films were scrutinized and the outline of the real left ventricular free wall border recognized on successive films.

Discussion

In the course of our initial angiocardiographic studies one of the most disconcert ing aspects encountered was the discrepancy in the calculated values of the muscle mass from film to film with n a given cardiac cycle. In most instances the magni tude of the changes was quite significant and obviously attributable to more than computational roundoff or simple measur ing errors. Since the parameter in these calculations in which we had the least confidence with respect to the techniques and accuracy of measurement was the wall thickness, a method was nvestigated whereby the est mate of this s ngle quan

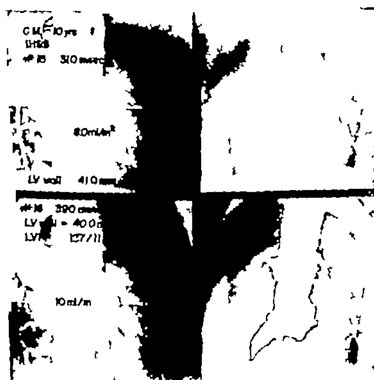


Fig 2 T films taken in late systole in patient with primary muscular hypertrophy (III S) #15 in end-systole (310 msec. after onset of contraction) and #16 during isovolumic relaxation. The wall hickened 77 per cent from diastole t systole On the PA film f int border of contrast material surround much clearer boundary ithin which the end-systolic volume is contained. Which is the correct one

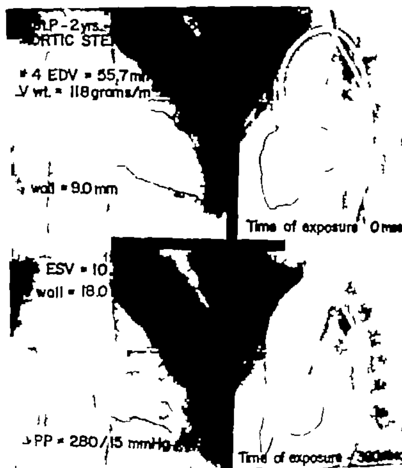


Fig. 3. End-diastolic and end-systolic films in a child with aortic stenosis. In the lower panel, direct measurement would have indicated a doubling of wall thickness (9 to 18 mm.). Fortuitously the catheter tip marks the true boundary of the ventricular wall. Computer predicted wall thickness (dashed line) coincides with the boundary indicated by the catheter tip.

ity might be improved upon. In observing the films which served as the input for the processing it was clear that the nearer in the time sequence that a film occurred relative to end-diastole the more distinct and easily measurable was the outline of the ventricular wall regardless of the lesion. In addition the geometry of the ventricular chamber at this point in the cardiac cycle most closely approximated the assumption of an ellipsoid of revolution which forms the basis for the mathematical model employed in this and other studies. Because of these considerations it was decided that the calculated value of the muscle mass (and hence the ventricular muscle volume) should be taken as that quantity computed for the film that was closest in time and just preceding end-diastole. This value for the mass was then held constant through all the other films in the cardiac cycle and the wall thickness appropriate for a given film computed in an analytic fashion.

Feigl and Fry[4] in direct measurements of the ventricular wall thickness in dogs by means of a caliper device found the increase during ventricular ejection to be an average of 20 per cent. Similar findings were reported by Hawthorne and co-workers[5] who saw an augmentation of the left ventricular wall thickness in ... from 0.08 to 0.10 cm. during systole. Mitchell and associates[6] in a study utilizing lead pellets implanted in the canine left ventricle and clips on the outside of the ventricular wall to demarcate the boundary of the inner shell of the free wall from the

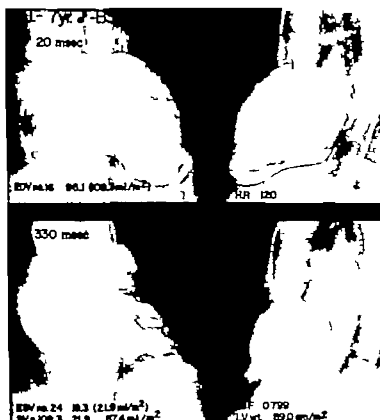


Fig. 4 End-diastolic (20 msec.) and end-systolic films (330 msec.) in 7 year-old boy with severe mitral regurgitation. Note that in the end-systolic film 2 boundaries can be recognized, one containing dense contrast, the other the dense contrast and volume including the papillary musculature marked by faint contrast. The predicted wall thickness marks the outer boundary

trabeculae, found the increase in wall thickness to be 25 to 45 per cent, whereas by standard angiocardiographic methods utilizing contrast media, the wall thickness varied from 80 to 120 per cent. Ross and co-workers[4] studied normal dog hearts rapidly fixed in end-diastole or end-systole and reported an average wall thickness that was 28 per cent greater in end-systole than in end-diastole. Furthermore, they found that papillary muscle volume averaged 14.7 per cent of the ventricular volume at end-systole. The most recent study was carried out by Lynch and co-workers, again in the dog utilizing rapid filming techniques at 540 frames per second. In his study the thickening in the wall was found to vary considerably from case to case, 15 to 50 per cent, with an average of 28 per cent.

This same degree of variability was present in the wall thickness of the first group of patients (10 individuals) where the predicted and the measured walls were virtually identical throughout the entire cardiac cycle. The measurements in individual cases increased by as little as 15 per cent and by as much as 64 per cent (Table I). However the average of these observations in 10 patients was 39.8 per cent, a figure considerably higher than that indicated by some of the animal studies but identical to that obtained by the only comparable and most reliable method that of Mitchell and associates.

Since most of the patients in this group had large end-diastolic volumes and smooth left ventricular walls throughout ventricular contraction, it is unlikely that there were any measurement errors in this first category. The discrepancy with the experimental animal data obtained in normal

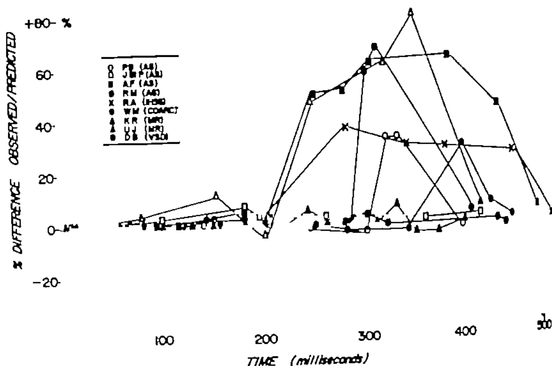


Fig. 5 Diagram plotting the per cent difference in observed ersus predicted wall thickness versus the time (film expos re) the observ tion was made 1 3 representative cases of each of the 3 groups (Table I) Note the discrepancies occur til after 200 msec. from the inscription of the QRS complex.

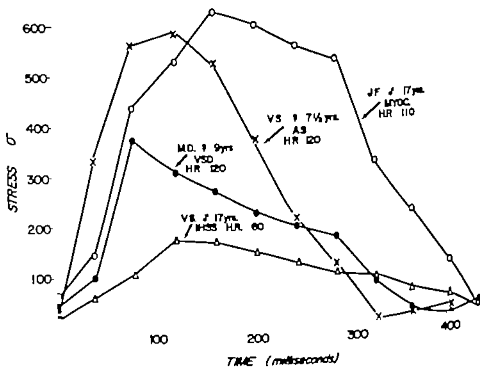


Fig. 6 Illustration of stress-time curves in 4 patient with different disorders (*high afterload* Patient V aortic tenosis P tient J F ch onic myocarditis *low impedance* P tient M D ventricular septal defect nd *variable fterload* P tient V S idiopathic hypertrophic subaortic stenosis with changing gradient) In all instances peak stress as reached before 200 msec after onset of contraction.

animals, therefore must be ascribed to the different species involved and to the virtual absence in our studies of anesthetic agents known to depress *myocardial* contractility and finally to the lack of any artifact that might be attendant to the use of calipers. In addition there may have been an inotropic effect of the contrast medium resulting in a more forceful ventricular contraction. Further evidence for the opinion that a different active state may have existed in the human data as a result of these interventions, as compared with the animal data is the fact that Feigl and Fry reported an increase of 30 per cent in systolic wall thickness in their dogs after infusion of norepinephrine.

Upon studying the increase in wall thickness in the other two groups, much larger discrepancies were found between the measured and predicted values. In fact, the average increase in the category where upon re-examination of the films, a second and less distinct boundary was detected *(Figs. 3 and 4)* was *73.8* per cent while in the last category (those patients where late systolic films failed to show any evidence of trapped contrast) the increase in systolic thickness compared to diastolic thickness was an average of 97.5 per cent. While this degree of thickening corresponds to that reported by Eber and co-workers (the average increase in their material was 100 per cent) the acceptance of systolic wall thicknesses of these dimensions would suggest a doubling of systolic muscle mass—a most unlikely occurrence. Plotting the wall thickness as a function of time of exposure of the films in three representative cases of each of the three groups (Fig. 5) it was seen that marked differences between measured and predicted wall thickness did not occur until 200 msec after onset of contraction or later in systole. Viewing the films and the evidence shown by Ross and co-workers that in dogs the papillary musculature and the trabeculae comprises 14.7 per cent of end-systolic volume versus only 5 per cent during end diastole, it appears most likely that erroneous inclusion of contracted trabeculae and of the papillary muscle mass, particularly during the later phases of systole will lead to the overestimation of systolic wall thickness. This error is most prevalent in those lesions where trabeculae and papillary muscles are well developed such as MR and AS, a fact which is confirmed by the preponderance of these lesions in groups 2 and 3.

These data lead to the conclusion that in the majority of these patients with a variety of congenital heart diseases it will be impossible by angiocardiography to judge the real free ventricular wall thickness accurately during the later stages of ventricular contraction and during end systole. Inclusion of infolding trabeculae and of the papillary musculature progressively squeezed dry of contrast material leads in these instances to a "pseudo" wall thickness measurement which exceeds the real wall thickness.

The significance of these observations lies in the fact that direct angiocardiographic measurements of wall thickness particularly after 200 msec of contraction in most lesions with hypertrophy cannot be accepted in the calculation of wall stress and of derived measurements such as the stress-strain relationships or ventricular modulus. On the other hand it should be emphasized that the analytic method outlined above for the derivation of the wall thickness remains only an approximation inasmuch as the measurement of the real dimensions of the inner cavity may also be affected by the exclusion of blood volume entrapped in the trabecular space. The extent to which this error will influence the angiocardiographically determined end-systolic volume and the derived ejection fraction has been discussed elsewhere.* It appears, therefore that unless clip measurements are available or other methods such as indicator dilution are employed end-systolic intracardiac and muscle volume measurements will have questionable accuracy. Computational methods in which the volume of the trabeculae and papillary muscula

*Measurements of end-systolic volume by fiberoptic indicator dilution technique at comparable heart rates were available in [illegible] patients, 3 in each group. End-systolic volumes in group [illegible] were higher by [illegible] per cent, in group [illegible] by 30 per cent, and in group 3 by 40 per cent. While in these patients end-diastolic volumes differed by less than [illegible] per cent. General regression equations describing the relationships between fiberoptic indicator dye dilution techniques and angiocardiographic determinations of end-systolic volume and end-diastolic volume have been given elsewhere.

ture is given a specific value which in turn is added to the predicted wall thickness are now being worked out. Finally it should be pointed out that for the calculation of peak stress and of data derived during isovolumic contraction such as the force velocity relationship the measurement of wall thickness is very accurate[13] since observations used in these calculations fall in the initial 200 msec of ventricular contraction and ejection during which wall thickness changes but little (Fig 6)

Summary

Measurements of the change in left ventricular wall thickness from diastole to systole by a variety of methods and in different species indicate unacceptable discrepancies (range 15 to 100 per cent) Since angiocardiographic methods are accepted more and more in the study of human heart disease the accuracy of this type of wall thickness measurement was investigated in 31 patients with representative examples of a variety of cardiac disorders with and without hypertrophy

A method was developed permitting the prediction of wall thickness on any film taken during the cardiac cycle End-diastolic muscle mass was considered the most accurate and its volume was assumed not to change during systole. Comparison of predicted and observed values for wall thickness showed complete agreement in 10 of the 31 patients. Average wall thickness increased 39 8 per cent. This result is in complete agreement with those reported by Mitchell and associates[5] in dogs in whom implanted radiopaque markers permitted accurate measurement of wall thickness during systole

In 10 of the remaining 21 patients the predicted wall thickness could subsequently be recognized during a careful re-examination of the films. In the remainder there was no way in which the true left ventricular wall could be recognized and wall thickness increased an average of 92.5 per cent. Similar figures have been reported by others. [12]

It is concluded that direct measurement of wall thickness during the second phase of ejection (after 200 msec. after onset of contraction) will lead to large errors, particularly in patients with hypertrophy. As a first approximation to a solution for this problem a computational method is described which showed complete agreement between observed and predicted values in all cases during the first 200 msec. after the onset of contraction.

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Relation of hemodynamics to height and weight percentiles in children with ventricular septal defects

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The association of growth failure and congenital heart disease has received extensive attention in the literature.[1-8, 11] While precise mechanisms for this phenomenon have yet to be elucidated study of large groups of children with congenital heart lesions has shown the following (1) severe growth retardation is more commonly associated with cyanotic lesions than acyanotic[4, 8] (2) in cyanotic lesions, height and weight were reported to be equally affected by some authors, while others noted a greater effect on weight[8] (3) in left to-right shunt lesions, weight is more severely affected than height and (4) in isolated pulmonic stenosis and coarctation of the aorta, while growth is most often normal height may be more affected than weight, giving rise to the stocky appearance usually associated with these lesions.[1, 8] Decreased systemic blood flow oxygen deprivation increased metabolic needs decreased absorption, and anorexia have all been suggested as possible mechanisms.[11] At the cellular level a decrease in cell mass and number has been noted in these children.[11] Finally some children with relatively normal physiologic data fail to grow at normal rates, suggesting a mechanism unrelated to their heart disease

In any group of children with congenital heart disease it is likely that growth failure is a result of multiple factors. In order to minimize the complexities it was decided to study a specific lesion and search for hemodynamic correlations with growth failure Children with isolated ventricular septal defects were chosen because this most common cardiac anomaly has a well-documented association with growth failure.

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Methods and materials

Cardiac catheterization data of 90 children with isolated ventricular septal defects were selected from a group of 119. These children ranged in age from 13 days to 16 years. Eight children were omitted because of multiple congenital anomalies, suspected rubella, and/or a proven chromosomal abnormality which might have been a factor in growth failure. Three were not included because general anesthesia was given during the procedure, and the data therefore could not be reliably compared. Thirteen were omitted because of technical difficulties encountered during the catheterization resulting in either inconsistent oximetry or failure to place the catheter in the pulmonary artery. Five children under 2 years of age with birth weights less than 2,500 grams were omitted because of the possible effect of prematurity on size.[1b]

Right atrial, right ventricular, and pulmonary artery pressures were measured in all children. Simultaneous pulmonary and systemic arterial oxygen saturations were obtained by the method of Van Slyke and Neill.[7] Lateral wall right atrial oxygen saturations were obtained either by additional Van Slyke-Neill determinations or cuvette oximeter readings calibrated with the Van Slyke-Neill samples from the pulmonary and systemic arteries. Pulmonary and systemic blood flows were obtained by the Fick method using measured oxygen consumptions in 28 patients and using estimated oxygen consumptions in the remainder. The data which involved the analysis of actual systemic and pulmonary blood flows rather than their ratios were confined to the 28 children with measured oxygen consumptions. When a left-to-right shunt could not be demonstrated by oximetry, relative pulmonary flows were determined from dye curve analyses using the double catheter sampling technique.[8] Two children in whom the calculated pulmonary flow was greater than five times the systemic were arbitrarily considered to have pulmonary to systemic flow ratios of 5 to 1, since the error involved in estimating shunts above this level is enormous.

Height and weight percentiles at the time of catheterization were determined for each child from the Boston Children's Medical Center Growth Chart. Values from Nelson's *Textbook of Pediatrics* were used for children age 13 and older.[9] These measurements were also expressed as a per cent of median height and weight for age. These percentages were used for computation of correlation coefficients.

The data were then key-punched onto IBM cards and analyzed using an IBM 360/50 computer. Predicted values for each child for systemic blood flow, oxygen consumption, and total pulmonary vascular resistance were computed using regression equations* derived earlier from measurements obtained on a group of normal children.[4] Height and weight percentiles for age were plotted against right ventricular end-diastolic pressure, mean pulmonary to systemic arterial pressure ratios ($\overline{PA}$/SA), pulmonary to systemic blood flow ratios (PBF/SBF), and systemic A-V oxygen differences. Height and weight percentiles of the 28 children with Fick determinations of cardiac output were also plotted against total pulmonary vascular resistance expressed as the per cent deviation from the predicted value, the ratio of systemic blood flow to the predicted value, and oxygen consumption to predicted oxygen consumption ratio. Plots of the latter two ratios against pulmonary to systemic flow ratios were also made.

Results

Table I shows the number of children for each year of age who had cardiac catheterizations. There are two definite periods which have the greatest number. Those under one year constitute one group and the second is comprised of children 4 to 6 years of age.

Table II shows the average height and weight percentile for the male and female groups individually and combined. The greater effect on weight is clearly seen with a mean percentile of 26 compared to [illegible] for height. In addition, the degree of growth failure was greater in the female than in the male group for both height and weight. A Z test analysis showed the d[illegible]

*Equations used were: systemic blood flow [illegible] (height) + 0.035 (weight) [illegible] (height) + [illegible] (weight) total pulmonary [illegible] = 3.80 + [illegible] (height) + 3.47 [illegible] vascular resistance = [illegible] + [illegible] (age) + [illegible]

Table I. No. of children by age (yr.) catheterized

Age	No. catheterized	Age	No. catheterized
<1	18	5	15
1	6	6	7
2	3	7	8
3	3	8	7
4	13	9 to 16	10

Table II. Average height and weight percentiles

	Males	Females	Both
Number	40	50	90
Mean weight percentile	33	19	26
Mean height percentile	43	31	36

ference to be statistically significant at the 1 per cent level for height, but only at the 10 per cent level for weight

A plot of weight percentiles against the ratio of mean pulmonary to systemic arterial pressure is shown in Fig 1 High pulmonary artery pressures were usually associated with low weight percentiles. When the mean pulmonary artery pressure was greater than 0 30 of the systemic only two children were above the twentieth percentile for weight Furthermore of the 27 children who had this degree of pulmonary hypertension, 22 (81 per cent) were at or below the tenth percentile for weight.

Fig 2 is a plot of weight percentiles against pulmonary to systemic blood flow ratios. High relative shunt flows were also associated with low weight percentiles, but not as uniformly as elevated pulmonary artery pressures. Of the 30 children with a PBF/SBF 2.0 1 or greater 23 (77 per cent) were at or below the tenth percentile for weight. The significance of this association is difficult to assess inasmuch as 18 of the 23 children with PBF/SBF 2.0 1 or greater also had $\overline{PA}/\overline{SA}$ > 0.30 The association of pulmonary hypertension and large shunts with poor weight gain was clear The correlation of weight percentiles with these parameters however was poor (r = −0.37 for mean pulmonary to systemic arterial pressure ratio and −0 27 for pulmonary to systemic blood flow ratio) It is noteworthy that the association of higher pulmonary artery pressures to poor weight gain bore no relationship to the total pulmonary vascular resistance. Plots of the per cent deviation from the predicted values of total pulmonary vascular resistance against per cent median height and weight for age showed no correlation (r = −0 19 and −0 07 respectively)

The large group of children who were small and yet had almost normal hemodynamic data was of interest. These cases accounted for the poor correlation There were 47 children who were at or below the tenth percentile for weight. Twenty-four (52 per cent) had $\overline{PA}/\overline{SA}$ < 0.30 and 24 (52 per cent) had $\overline{PBF}/\overline{SBF}$ < 2 0 1 18 (38 per cent) were below both these levels.

Fig 3 shows there were major differences in the data when the two age periods with the greatest number of patients were analyzed separately Of the 18 children under one year of age 16 (89 per cent) were at or below the tenth percentile for weight Moreover only 2 had a PAM/SAM < 0 30 In the 4 to 6 year group, however there were 28 children of whom 8 (29 per cent) were at or below the tenth percentile for weight. Six of the 8 (75 per cent) had a PAM/SAM < 0 30

An interesting finding in the children with measured oxygen consumption was the tendency for systemic blood flow to be less than the predicted values in children with larger shunts Fig 4 is a plot of systemic blood flow to predicted systemic blood flow ratio (SBF/PSBF) against PBF/SBF As seen when the PBF/SBF ratio was less than 1.5 1 the observed values were equally distributed about the normal predicted values (1 00) As the magnitude of the shunt increases the SBF/PSBF ratio decreases, so that only one of 15 children with PBF/SBF ratio > 1.5 1 had a SBF/PSBF greater than 1 00

This group of children comprised only 28 of the total number and was further

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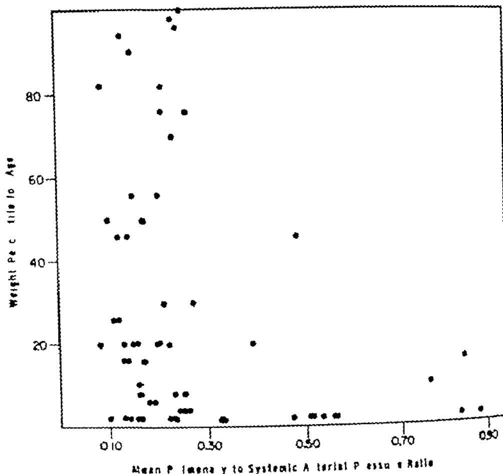


Fig 1 A plot of weight percentiles against mean pulmonary to systemic arterial pressure ratios.

selected inasmuch as their ages were from 4 to 16 years. Their mean age was 7.5 years and therefore in general represented patients whose conditions did not warrant a catheterization earlier in life

Discussion

One of the inherent difficulties in a study such as this is the recognition that growth has been affected This is not difficult in its most severe form. Normal variation in height and weight for any given age however makes moderate degrees of growth failure difficult or impossible to ascertain in the individual This can be overcome to some extent by the use of large numbers. A moderate effect on growth can then be determined for the group although caution must be used in the interpretation of such data.

In this group of patients there is significant growth failure in both height and weight with a clearly greater effect on weight. More surprising is the greater degree of growth failure in the female group regardless of the etiology The difference between the males and females is apparently greater for weight, but because of the large standard deviation in this parameter it is statistically significant at a lower level of probability than height.

In children with this lesion it is apparent that a hemodynamic alteration cannot be implicated as the sole factor in growth failure. However children with moderate degrees of pulmonary hypertension (i.e., a mean pulmonary to systemic arterial pressure ratio greater than 0.30) are small. This is true whether the hypertension is secondary to increased pulmonary vascular resistance or to increased pulmonary blood flow This has been observed previously but a causal relationship has yet to be proven.[9,11]

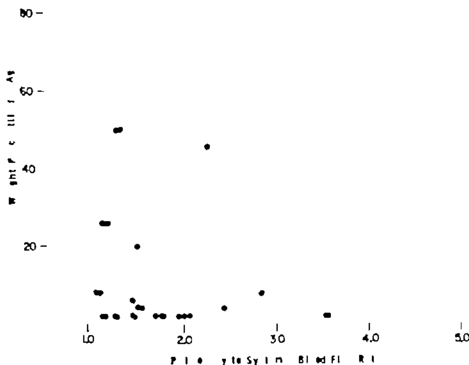


Fig. 2. A plot of weight percentiles against pulmonary t systemic blood flow ratios.

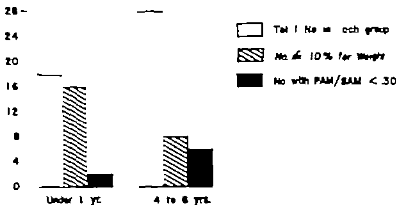


Fig. 3. Separation of data by age groups. (Not small proportion of children under one year with PAM/SAM < 0.30.)

More striking however is the number of children in the lower percentile ranks who do not have significantly abnormal hemodynamic data as presently defined. This was most apparent in the 4 to 6 year age group where three fourths of the children who were below the tenth percentile for weight had essentially normal pulmonary artery pressures. This phenomenon would appear to implicate some

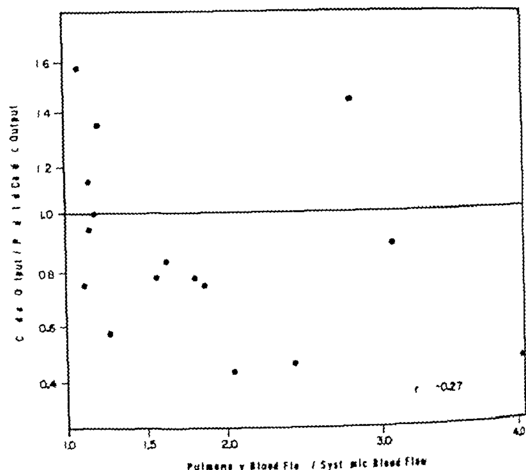


Fig. 4. A plot of measured cardiac output to predicted cardiac output (systemic ... predicted systemic blood flow ... tios) against pulmonary to systemic blood flow ratios.

factor(s) in these children as a cause of growth failure. It is possible though that in some of these cases the hemodynamic alteration may have been more severe earlier in life. This could have caused a detrimental effect on growth rate which might not have been overcome later.[11] The majority of children under one year of age who had growth failure and abnormal hemodynamic data would support such a concept. However, it is more likely that this finding has occurred because of our criteria in selecting patients for catheterization. Our group routinely catheterizes infants suspected of having ventricular septal defects with severe hemodynamic alterations.

Since the systemic blood flow reportedly is normal in the presence of congenital heart disease except in advancing age and in the presence of congestive heart failure[4,5] a consideration of this seems especially germane. It is logical to assume that in any chronic condition the systemic blood flow and body size will be commensurate. If this is true, the observed systemic blood flow by necessity will generally be normal when compared to the predicted values since height and weight are the parameters used in deriving the predicted values. Even when these parameters are used, however, our data suggest a tendency for systemic blood flow to be less than normal in the presence of left-to-right shunts greater than 1.5:1. Significantly abnormal hemodynamic data, however, as presently defined, do not account for a large group of children with weights below the ... percentile.

Summary

Cardiac catheterization data of 90 children with isolated ventricular septal defects were analyzed for hemodynamic correlates

with growth failure. Growth retardation (weight more than height) was a prominent feature in both sexes although girls were more severely affected

Of the hemodynamic parameters measured none correlated well with growth failure. There was, however a close association between pulmonary hypertension and poor weight gain. The antithesis was not true Over half of the children below the tenth percentile for weight had pulmonary to systemic pressure ratios of 0.30 or less, precluding good correlation

It is believed that significantly abnormal hemodynamics in children with isolated ventricular septal defects in this age group do not account for a large proportion of growth failures.

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Case reports

Single ventricle with normal relationship of the great vessels and pulmonic stenosis

A case report of an adult with the "Holmes heart"

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The incidence of single ventricle in large series of congenital cardiac malformations has been found to be approximately 3 per cent.[1] An anatomic classification of single ventricle has been made by Van Praagh and his associates[2] in which four discrete subgroups are recognized: type A, single left ventricle (absent right ventricular sinus); type B, single right ventricle (absent left ventricular sinus); type C, undivided ventricular sinuses (absent or rudimentary ventricular septum); and type D, infundibulum only (both sinuses absent). They further subdivided these types according to the presence or absence of transposition of the great arteries and a normal or inverted location of the viscera.

Pulmonary stenosis may occur in all types of single ventricle. However, the association of pulmonary stenosis with normally related great arteries is quite rare; only 15 cases have been described.[3-14] The prognosis of patients born with a single ventricle is generally poor. Only [illegible] cases have been reported to survive beyond the age of 21.[1,4,13,17,21-23]

We recently encountered a 26-year-old patient with single ventricle and a normal relationship of the great arteries and [illegible] viscera who had associated severe pulmonic stenosis. The findings in her case and the good result of surgical intervention form the basis of this report.

Case report

P. R., a 26-year-old woman, was admitted to the Barnes Hospital on Feb. 16, 1968, for evaluation of cyanotic heart disease. Her [illegible] recalls that the patient had been cyanotic since infancy. When the patient was 12 years of age, an angiocardiogram performed elsewhere was interpreted as showing [illegible] tetralogy of Fallot. Surgical correction was proposed but declined. She attended [illegible] school for handicapped children and completed the [illegible] grade at age [illegible] teen. She had [illegible] normal menarche but subsequently had menorrhagia. Until six months prior to admission she [illegible] able to participate in [illegible] activities which included bicycle riding. She then began to have increasing dyspnea on exertion,

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ness, and occasional hemoptyses. She was intermittently given digitalis and diuretics without improvement. At the time of admission she was only able to walk very slowly on level ground.

On admission, the patient was a deeply cyanotic, well-developed white female in no acute distress. Her blood pressure was 150/115 mm. Hg in both arms and 190/110 mm. Hg in the right leg. The pulse was regular at 110 beats per minute and the respirations were 20 beats per minute. She had facial acneform rash with marked cyanotic coloration. The retinal veins were moderately engorged. The jugular veins were not distended; normal waves could be seen. The chest was of normal configuration and was clear to auscultation and percussion. Examination of the heart revealed a left parasternal lift with a palpable second sound. A systolic thrill was palpable at the fourth left intercostal space. The left border of cardiac dullness was in the midclavicular line. The first sound was normal; the second sound was single and somewhat accentuated. A Grade 4/6 harsh holosystolic murmur was heard maximally at the fourth left intercostal space along the sternal border; it radiated to the entire precordium and to the back. The murmur increased with inspiration. No diastolic murmur was heard. No hepatosplenomegaly was detected. She had marked cyanosis and clubbing of the fingers and toes. The neurological examination was within the limits of normal.

The hemoglobin was 26.1 Gm. per cent, the hematocrit 84 per cent, and the red blood cell count was 8,620,000 per cu.mm. The white blood cell count was 8,400 with a normal differential, and the platelets were 81,000. Urinalysis demonstrated trace proteinuria but was otherwise unremarkable.

Roentgenograms showed borderline cardiomegaly (Fig. 1). The pulmonary artery was small and the pulmonary vasculature was slightly decreased. An electrocardiogram (ECG) demonstrated sinus arrhythmia, +30° mean frontal QRS axis, left ventricular enlargement, and S-T and T-wave abnormalities. Sharp 2.5 mm. P waves were present in Lead II (Fig. 2). The vectorcardiogram showed left ventricular enlargement with S-T and T-loop abnormalities.

With a saline infusion running, phlebotomy of one unit of whole blood was performed. Twelve hours later a second unit of blood was removed over a 30 minute period. Following this procedure, the patient's blood pressure fell to a palpable systolic pressure of 90 mm. Hg. She had tachycardia and peripheral vasoconstriction. Fresh frozen plasma was given and the vital signs returned to normal. Thereafter all phlebotomies were performed with the simultaneous infusion of plasma. Because of the patient's high hematocrit, plasmapheresis was not feasible. At the time of cardiac catheterization, the hematocrit was 71 per cent.

Cardiac catheterization was performed from the right median basilic vein. The catheter advanced through the normally located great veins and right atrium, then passed into the high pressure ventricle in the characteristic manner for crossing the tricuspid valve. The catheter formed a low broad sweep across the cardiac shadow and passed int



Fig. 1. *A* and *B*. Admission chest roentgenograms.

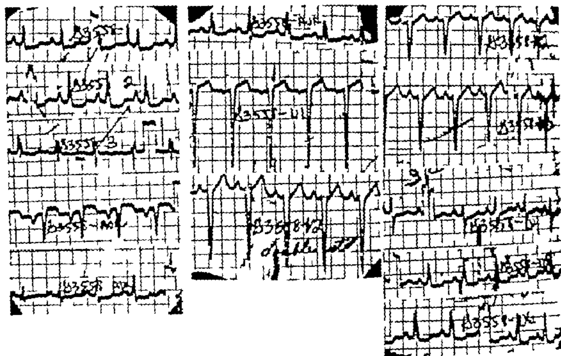


Fig 2 Ad vs on lc d agram

the scend t The theter ould not be ma pi l ted t h pulm ia artery Recorded pre- ere rcle 150 0 8 mm. Hg aorta, 150 110 m Hg ri ht tri m mean 4 mm Hg Ox gen sat n de erm nation were superior en 48 5 per t right trium 52 per cent ventricle 55 5 nd 59 per cent ascending aorta, 67 5 and 63 5 per ce t The ight to-left shunt ap pr x mated 70 per ent A h dr gen inhalation urve h wed h ppear or the right atrium. Angio ard gr m re made th njection of contra t med m t the scend ng aorta nd into the pex of the ventricle sing the biplane oll film technique (Figs. 3 nd 4 A single entricle was found to be of left entricular m rpholog An infundibular outflow chamber ituated a normal ntero-superior position The aorta and pulmonary artery were in normal lationsh p M rkedly diminished pulmonary blood flow w present A small bulbo-ventricular foramen as present ith a hypoplastic nfund bular chamber and distorted thickened pulmonic val indic t ng obstruction to pulmonary flow t several lev l The oronary arteries were seen to be of normal o g nd distribution An aberrant right subcla ia artery arose f om the distal aortic arch These finding onform to the angiographic description b H Hermann and as sociates[24] for single entricle ith pulmonic ste nosis nd a normal relationship of the great vessels types A through I of V P augh classification.

Phlebotomy wa continued ntil hematocrit of 60 per cent w reached t which time the patient underwent surgery At the time of operation per formed by Dr Thomas Ferguson the retro-esophageal berrant right subclavian artery was identified. The main pulmonary artery was 1.5 cm in great diameter A Potts-Smith shunt as created th 5 to 6 mm. ortic pulmonary artery anastom The patient had no postoperativ complication and was discharged two weeks following surge

On her most recent clinic visit, t o months after the operation, the cyanosis had virtually disappeared, the blood pressure had fallen to normal, the hem tocrit was 46 per cent, and the arterial oxyg saturation was 92 per cent. The ECG was unch from the preoperative tracing She reported dr matic symptomatic improvement.

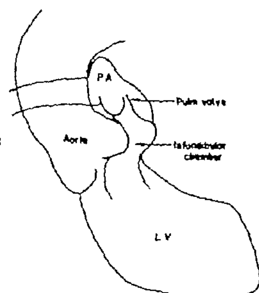
Discussion

To the best of our knowledge only ?? cases of single ventricle in which the pa tients survived beyond the age of 21 hav been reported ... Rahimtoola and co-workers had 5 patients, "aged 15 ... but exact ages were not specified and the cases are not included. All of these patients except Holmes original ca had abnormal relationships of the great arteries The oldest died at 56 years single ventricle and a truncus arterio

The pulmonary outflow tract was sp cifically described in 17 patients and found to be stenotic in 12 It has been proposed that pulmonary stenosis enhances su vival[7,81] However Rahimtoola's group could make no conclusions as to the effect







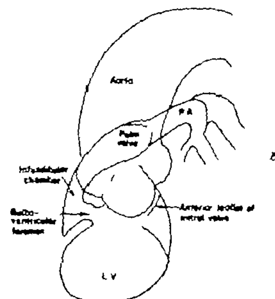


Fig. 3. A and B. Anteroposterior angiocardiogram after injection of contrast medium into apex of single ventricle.

Fig. 4. A and B. Lateral angiocardiogram after injection of contrast medium into apex of single ventricle.

in their series, which consisted of children primarily, and our review of the few patients surviving beyond age 21 is also indecisive.

The growth and development of most of the long term survivors was surprisingly normal. One patient even survived three pregnancies.[18] In the 17 cases in which cyanosis was mentioned, 13 were cyanotic from birth or early infancy. Although our patient had a different anatomic defect, she conformed to this pattern with deep cyanosis from birth but an otherwise completely normal growth and development.

Holmes[1] first described single ventricle with normally related great arteries and pulmonic stenosis in 1824. Since that time

only 14 additional cases have been recorded. The oldest in this group was Holmes' patient who died at 22 years of age. 7 of the patients were specified as infants. Thus, to our knowledge, our patient is the oldest survivor with this variant of single ventricle.

Two conditions which can be confused with a "Holmes heart" are tetralogy of Fallot and tricuspid atresia.[13] Our patient was thought to have a tetralogy on clinical grounds until the ECG was examined. Pure left ventricular hypertrophy without signs of right ventricular hypertrophy is not seen in tetralogy with predominant right-to-left shunt.[17] The typical route of the catheter in crossing the tricuspid valve and the failure to cross the left atrium before entering the ventricle appears to exclude tricuspid atresia.

The ECG findings in single ventricle have been quite varied. Although the ECG may reflect only position in the thorax, Van Praagh and associates[12] demonstrated that the pattern generally corresponded to the actual ventricular anatomy. Thus, when the single ventricle was left-sided, the ECG almost always showed a normal axis or left axis deviation and the pattern of left ventricular overloading was usually seen, although biventricular overload was also noted. A right ventricular overload pattern was not seen when the ventricle was left-sided.

There is little information on the ECG patterns in the "Holmes heart." The patient reported on by Rosenquist and associates showed left axis deviation and left ventricular hypertrophy on the vectorcardiogram. The patient discussed by Van Praagh and associates[12] had left ventricular hypertrophy and a normal axis with right atrial hypertrophy. One of the patients of Elliott and associates also had left axis deviation and left ventricular hypertropy, but the other had right ventricular hypertrophy and high voltage mid precordial R S complexes.[17] Our patient had a normal axis and left ventricular hypertrophy on the standard ECG and vectorcardiogram. The peaked P waves in Lead II might reflect right atrial hypertrophy, although other explanations are possible.[3]

Physical findings have been described in 10 patients. All patients were cyanotic at birth or in infancy except two, who became cyanotic at two[7] and five[11] years. All had systolic murmurs at the left sternal border; one[7] also had a thrill similar to our patient. The second sound has not been previously reported to be single.

No previously reported patients with "Holmes heart" have been noted to have systemic hypertension. The fact that our patient did, and that it disappeared with reduction of the hematocrit following surgery, might raise speculation about the mechanisms involved. Several experimental observations may be pertinent to an understanding of the hypertension in this case. Putman and co-workers[24] showed that the viscosity of blood with a hematocrit of 82 per cent is increased fivefold over blood with a hematocrit of 44 per cent when measured in a system comparable to that present in small arterioles. Verel demonstrated that the total blood volume in the polycythemia of cyanotic congenital heart disease is only slightly increased. He further showed that while the red cell volume is elevated, the plasma volume is correspondingly reduced.

These clinical findings can be roughly duplicated experimentally by the induction of normovolemic polycythemia in a dog with a normal cardiovascular system. In this preparation, the resistance is found to be markedly increased, the cardiac output is reduced, and the mean arterial pressure is essentially unchanged. Because increased resistance of the same degree is found in both the pulmonary and systemic circulations, it has been suggested that the high viscosity—not vasomotor tone—is a significant contributing factor. Any advantage obtained from an increase in oxygen-carrying capacity is apparently offset by a disproportionate fall in cardiac output.[14] Replogle and associates have suggested that the greatly increased red cell concentration in hypoxemic patients might represent a homeostatic mechanism that has overcompensated and become a liability.

Although the validity of extending and applying these observations to the clinical problem under discussion is not established, it might be hypothesized that the increase in systemic arterial pressure represented a compromise between the various ph

logical control mechanisms alluded to above in an attempt to maintain homeostasis in a uniqu pathologic setting

Rahimtoola and associates[14] demonstrated the presence of favorable streaming in 11 of their 19 patients with single ventricle without pulmonary stenosis to the extent that the more oxygenated blood tended to flow out the aorta. The pulmonary artery was catheterized in only 1 of their 12 patients with severe pulmonary stenosis. All but one of this latter group had over 30 per cent right-to-left shunt and arterial oxygen saturations less than 68 per cent. They theorized that the severe pulmonic stenosis would promote more complete mixing in the ventricle and allow much less streaming therefore, the cyanosis would be more severe. Although the pulmonary artery was not entered in our patient, favorable streaming might be inferred from the difference in oxygen saturations in the ventricular and aortic samples.

Analysis of our patient suggests that she had always had just enough pulmonary blood flow possibly aided by favorable streaming to permit her to lead a relatively normal albeit restricted life. For some reason, this tenuous balance was upset a few months before she was seen and gradual decompensation ensued. When the other reported patients with this anomaly are considered it is remarkable that she did so well for this long. It was apparent that a systemic-pulmonary shunt procedure to improve the arterial oxygen saturation represented the only chance for a significant long term improvement.

Because of the well-known operative complications in cyanotic polycythemic congenital heart disease[13] cautious phlebotomies were performed on our patient. Phlebotomy without concomitant volume replacement in the setting of a normal or slightly elevated total blood volume in a barely compensated circulation would theoretically invite the complication of inadequate regional perfusion in fact, this occurred when our patient was first subjected to phlebotomy. It was avoided in subsequent efforts by the concomitant infusion of a colloid. She went to surgery with a hematocrit of 60 per cent and no complications occurred.

Summary

A 26-year-old patient with single ventricle normal relationship of the great vessels, and pulmonic stenosis is reported on. This is only the second patient with this lesion over age 21 to be described the other being Holmes original case as reported in 1824 who died at 22 years of age. A Potts-Smith anastomosis has greatly improved the patient's exercise tolerance and oxygen saturation of the arterial blood.

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Pseudotruncus arteriosus

Report of the oldest surviving patient

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Pseudotruncus arteriosus is a severe variant of tetralogy of Fallot with atresia of the pulmonary arteries and pulmonary blood flow supplied through collateral blood vessels provided usually by enlarged bronchial arteries. Although the majority of these patients die early in infancy, rare survivals to the third decade have been recorded.[1-4] The following is a report of the oldest living patient found in the literature.

Case report

A 43-year-old housewife with a known history of cyanosis and heart murmur since birth was admitted to the Henry Ford Hospital with a three week history of postural vertigo and fatigue. The patient also complained of dyspnea, palpitations, and increased cyanosis with efforts, but was still able to do most of her housework at a slowed pace. There was no history of anoxic spells, syncope, squatting or angina. She was treated for endocarditis in another hospital at age 21 years and for pneumonia at age 35. The patient had had two normal pregnancies and two miscarriages.

On examination the patient appeared as a well-developed, middle-aged woman in no distress, with mild cyanosis and clubbing of the fingers and toes. The blood pressure was 130/60 mm. Hg, pulse 80 beats per minute and regular, temperature 98.6° F, weight 112 lb., and height 62 inches. There was a prominent low parasternal lift. The apical impulse was palpable at the sixth intercostal space at the level of the left anterior axillary line. The first sound was well preserved and the second sound was accentuated and single. There was an early ejection systolic click and a loud continuous murmur could be heard over the precordium, becoming more intense at the right second intercostal space and radiating to the infraclavicular and left interscapular areas.

Laboratory data

The hemoglobin was 17.2 Gm. per 100 ml., the leukocyte count was 6,950 per c.mm. with a normal differential. The urinalyses, fasting blood sugar, blood urea nitrogen, and creatinine were normal. The serologic test for syphilis was nonreactive. The electrocardiogram (Fig. 1) revealed changes indicating right ventricular hypertrophy. Chest fluoroscopy showed the typical coeur en sabot configuration with markedly diminished pulmonary artery shadow, decreased pulmonary vasculature, cardiomegaly, and right aortic arch (Fig. 2). The prominent bronchial arteries were shown in the lateral view (Fig. 3) indenting the barium column. Enlargement of the right ventricle was also noted.

At cardiac catheterization (Table I) the aorta was entered easily from the right ventricle. The right ventricular and systemic systolic pressures were equal and there was desaturation of the arterial blood to 84 per cent.

The cineangiocardiogram from the right ventricle showed (Fig. 4) rapid filling of the ascending

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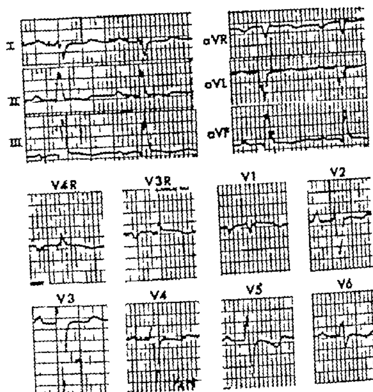


Fig. 1 The electrocardiogram shows right axis deviation with a tall R in V_{4R} and V_{3R}.

orta and left ventricle and there was no visualization of the pulmonary infundibulum or arteries. A selective cineangiocardiogram (Fig. 5) of the descending aorta demonstrated filling of the very large bronchial arteries without retrograde visualization of the main pulmonary artery or its branches.

Discussion

It is widely recognized[3-7] that the differential diagnosis between a pseudotruncus and a truncus arteriosus Type IV of Collett and Edwards[8] with absent pulmonary arteries is often impossible on clinical radiologic or hemodynamic grounds. In both instances only one large artery may be shown arising from the base of the heart without pulmonary arteries and the pulmonary blood flow is supplied by bronchial arteries or other collaterals. The angiocardiography is very helpful in those cases where the branches of the pulmonary arteries fill in a retrograde fashion by way of systemic pulmonary anastomoses establishing the diagnosis of pseudotruncus. In our patient the pulmonary arteries were not visualized and the markedly enlarged bronchial arteries were supplying the blood to the lungs.

Recently Van Praagh and Van Praagh in their study of 57 necropsy cases of truncus arteriosus communis, reached the conclusion that truncus with a ventricular septal defect is tetralogy of Fallot with pulmonary atresia, plus partial or complete absence of the aorticopulmonary septum. They offered a new classification of truncus arteriosus excluding Collett and Edwards Type IV which they consider to be a solitary aorta with absent

Table 1 Cardiac catheterization data

Site	*Pressures (mm. Hg)*		O_2 *content* (vol %)	O_2 *sat* (%)
	S/D	*Mean*		
Superior vena cava	—	3	16 3	71
Inferior vena cava	—	3	16 3	71
Right ventricle	148/4–12		17 5	76
Brachial artery			19 1	83
Central aorta	146/54	89	19 3	84

S/D, Systolic/Diastolic; Sat., saturation.

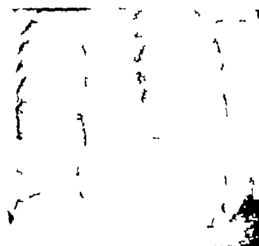


Fig. 2. Posteroanterior chest roentgenogram shows cardiomegaly with markedly decreased main pulmonary artery shadow, diminished vascularity, and right aortic arch.



Fig. 3. Lateral roentgenogram showing two indentations in the barium column at the level of the bronchial arteries.

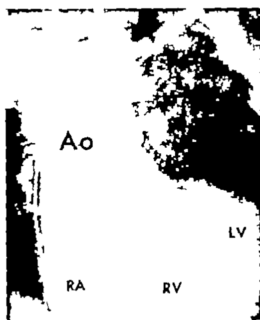


Fig. 4. Angiocardiogram with injection into right ventricle (*RV*). Contrast medium outlines right aortic arch (*AO*), part of the left ventricle (*LV*), and right atrium (*RA*).



Fig. 5. Single frame from cineangiogram. Lateral view of the descending aorta (catheter tip above arrow) showing the filling of the markedly enlarged bronchial arteries from the aorta (arrow).

of the pulmonary artery and its branches as was suggested first by Manhoff and Howe.[14] In view of the lack of anatomopathologic confirmation in the present report, this patient could also have been considered as an example of a solitary aorta with atresia or absent pulmonary arteries. In either case this patient represents, to our knowledge, the oldest surviving example of one of these two similar anomalies.

Long survivals of patients who have tetralogy of Fallot are not unusual, but as stated by Rowe and associates, very few cases in their natural course live to the second decade with an average life expectancy of 12 years. The incidence of more severe forms of tetralogy of Fallot

with pulmonary atresia (pseudotruncus arteriosus) was found to be 23 per cent in a recent review of a total of 418 patients with tetralogy.[15] The same authors noted that in their own series of 128 cases of tetralogy, 36 patients with pulmonary atresia were included and of this group, 22 died during the first year, 7 of them following surgery. The average survival age among the 115 cases of tetralogy of Fallot reported by Abbott[13] was 12 years, including 30 patients (26 per cent) with pulmonary atresia with a survival rate ranging from 9 days to 30 years.

The number of patients with pseudotruncus reaching or exceeding the third decade is very limited, and in a review of the literature we have found a total of 5 examples.[5] The oldest of this group was known to be alive at the age of 38 years in December, 1966.[4] The survival time in pseudotruncus is directly proportional to the volume of systemic pulmonary collateral blood flow, and large bronchial arteries were uniformly present in the small group surviving to the third decade.[4,5]

Shunt procedures have been performed with some improvement in a few selected cases of pulmonary atresia, provided the pulmonary arteries are of adequate size.[15] Another palliative procedure which has been recommended is that of pleurectomy to increase the pulmonary blood flow and stimulate systemic-pulmonary precapillary anastomosis in patients with cyanotic congenital heart disease with a decreased pulmonary blood flow and low pulmonary artery pressure. In the case here reported, we have elected to follow the patient conservatively in view of the fact that she has been doing reasonably well with adequate collateral flow by way of the very large bronchial arteries. The lack of demonstrable pulmonary arteries would contraindicate shunt or other corrective surgical procedures.

Summary

A 43-year-old housewife with pseudotruncus arteriosus was presented and is believed to be the oldest individual with this anomaly described in the literature.

An early ejection click, a continuous heart murmur heard over the precordium and left scapular area, mild cyanosis, and clubbing of the fingers and toes were the main clinical features. The difficulty in the clinical differential diagnosis from a truncus arteriosus with absent pulmonary arteries was emphasized.

The authors would like to express their appreciation to Dr. Robert S. Ormond for reviewing the x rays and angiocardiograms.

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Crural hypertension in abdominal aortic coarctation

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Within the last two decades a number of cases of coarctation of the abdominal aorta have been reported bringing the total number to 78,[1] but a careful analysis shows that only three patients[2] had elevated blood pressure in the lower limbs. Elevated blood pressure in the lower limbs in cases of coarctation poses a diagnostic problem.

Case report

A 16-year-old girl was seen earlier this year with a history of intermittent headache for six months. Two years ago during investigation of pauciarticular ankylosing(?) aortitis, an x-ray film of the chest had revealed tuberculous infiltration about the right apex. She was treated with antituberculous chemotherapy. Subsequent x-ray films had shown complete resolution of the lung lesion.

Physical examination revealed elevated blood pressure. Subsequent blood pressure readings varied from 180 to 220 mm. Hg systolic and 130 to 160 mm. Hg diastolic in both arms. The femoral pulses were palpable bilaterally. Blood pressure in the legs varied from 190 to 230 mm. Hg systolic and 140 to 180 mm. Hg diastolic. The superficial epigastric artery was not seen or palpable. A systolic bruit was heard 3.5 cm. above the umbilicus a little to the left of the middle line. Funduscopy showed swelling of the discs (1 diopter) in both eyes, arteriovenous nipping, a patch of hemorrhage in the inferior temporal angle of the left eye, and a macular star in the same eye. The rest of the physical examination was noncontributory. The investigations performed and their results are as follows: Mantoux, positive 1 in 1,000; urine culture, sterile; blood urea, 27 mg. per 100 ml.; serum calcium, 11.8 mg. per 100 ml.; serological test for syphilis, negative; urine chromatography, negative for catecholamines.

A chest x-ray (Fig. 1) showed that the cardiac contour was within normal limits and the lung fields were clear. There was no evidence of rib notching. An electrocardiogram revealed left ventricular hypertrophy and strain.

An intravenous pyelogram (Fig. 2) showed good function in the left kidney and delayed and diminished excretion from the right. The right kidney appeared hypoplastic, while the left appeared enlarged. Cystoscopy revealed normal bladder and ureteric orifices. Retrograde pyelographs showed flattened pelvicalyceal pattern on the right side.

A right femoral retrograde aortogram showed that the catheter could not be passed beyond the level of the third lumbar vertebra. Following introduction of dye, aortic narrowing was visualized at the level of the third lumbar vertebra (Fig. 3). The dye reached the superior mesenteric system through the upper left colic branch of the inferior mesenteric artery.

A left brachial retrograde angiogram showed an obstruction at the level of the second lumbar vertebra (Fig. 4). The left renal artery was visualized and later pictures showed opacification of the left renal calices and ureter. The right renal artery was not seen but later pictures showed faint traces of dye in the major calices of the right kidney.

Discussion

Coarctation of the aorta may be present anywhere in the thoracic or abdominal segment. Abdominal coarctation appears relatively uncommon compared to the thoracic coarctation. Coarctation of the abdominal aorta appears to occur more frequently in females in contrast to the male predomi

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Fig 1 Radiograph of chest. Cardiac contour normal. No evidence of rib notching.



Fig 2 Intravenous pyelogram. Normal excretion in left kidney. Diminished and delayed excretion in right kidney.

nance in thoracic coarctation.[1] Involvement of the visceral arteries in abdominal coarctation provides a varied symptomatology but also renders treatment difficult. Coarctation of the aorta may be congenital or acquired, single or multiple. Congenital coarctation is thought to be due to failure of the two primitive dorsal aortas to fuse, followed by disappearance of one of these. Acquired coarctation includes cases of local arteritis including periarteritis, and that form which has been described in young women as pulseless or Takayasu's disease.[4] This is characterized histologically by collections of chronic inflammatory cells including giant cells. The distinction between congenital and acquired disease may be difficult to make since varying degrees of atherosclerosis, intimal and medial thickening and adventitial fibrosis are often observed adjacent to the site of congenital coarctation in young adults.[1] The history and subsequent course with the development of similar lesions in major peripheral arteries reveal the true nature of such cases. The stenosis may be localized or there may be diffuse narrowing or hypoplasia of the abdominal aorta extending as far as its bifurcation.[4] According to Tansig,[7] patients are usually asymptomatic in childhood, which suggests that the proximal segment of aorta does not increase in diameter as the aorta grows, thereby the constriction becomes proportionately greater as the individual attains growth.

The manifestations of abdominal coarctation and treatment depend upon the site of coarctation, involvement of visceral branches, and the efficiency of the collateral circulation. Among the symptoms of headache, palpitation, dyspnea, giddiness, and tiredness, headache seems to be the most frequently recorded.[8] Other symptoms include abdominal angina and peripheral arterial insufficiency in the lower limbs. Vascular insufficiency symptoms like intermittent claudication, poor development of the lower limbs and gangrene are comparatively less common in abdominal coarc-



Fig. 3 Right femoral retrograde aortogram. Obstruction of aorta at the third lumbar vertebra. Dye reaches superior mesenteric system through upper left colic branch of inferior mesenteric artery



Fig. 4 Left brachial retrograde angiogram. Obstruction of aorta at the second lumbar vertebra. Left renal artery is visualized. Collaterals are seen on left side. Right renal artery not seen. Faint traces of dye are seen in the right kidney

tation. Collaterals appear better developed on the left side in abdominal coarctation whereas in thoracic coarctation they are better developed on the right side. The larger area occupied by the liver on the right side in the abdomen and the heart occupying the left hemithorax probably account for the variation. The femoral pulse on the right or both sides may be absent or weak. However normal femoral pulses have been recorded.[1] Rib notching may be absent or confined to the lower ribs. The coarctation murmur may be localized or heard over a wide area extending from the xiphisternum to the umbilicus anteriorly[4] and posteriorly from the tenth dorsal to the third lumbar spine. The murmur is better appreciated with the diaphragm firmly applied to the surface of the body and is likely to be missed with the bell of the stethoscope applied lightly.

Most cases of coarctation have hypertension in the upper extremities and hypotension in the lower extremities. However the blood pressure in the lower extremities may be normal or occasionally elevated in the left lower limb alone[3,1] or along with the right. Hypertension in the left lower limb alone is associated with efficient collaterals on that side. Hypertension may be persistent or paroxysmal, simulating pheochromocytoma, probably due to increased blood supply to the adrenals through the collaterals producing functional hypertrophy of the adrenals. Goldzieher and associates[3] found a large system of distended collateral vessels, including the adrenal vessels, in a patient with coarctation of the abdominal aorta who presented with paroxysmal hypertension. At opera-

tion collaterals appeared better developed on the left side. Hypertension associated with coarctation of the abdominal aorta may be caused by the coarctation alone or due to associated unilateral or bilateral renal ischemia.[1,13] Renal vessels may be involved in the coarctation itself by associated arteritis or due to atherosclerotic plaques involving the origin of the vessel.[14] The diagnosis of coarctation is fairly evident with hypotension in the legs, but not so obvious with lower extremity hypertension.

Routine urinalysis and an intravenous pyelogram are helpful as screening tests. Urinalysis may be abnormal, but in the face of normal urinary findings in a young person with high blood pressure and severe retinal changes, one should keep the possibility of renovascular hypertension in mind. An excretion pyelogram can be helpful if it shows delayed or diminished excretion on one or both sides. The diagnosis is confirmed by angiography. Angiograms may be performed through the femoral, brachial, or translumbar routes. Of these, the retrograde femoral aortogram appears to be advantageous as the dye remains for a comparatively longer time and brings out the collaterals very much better delineated.

Treatment consists of resection and reconstruction or bypass operation. Resection may be performed for localized coarctation without involvement of the visceral arteries. Bypass operation is indicated for longer segments, multiple constrictions, or involvement of visceral branches, i.e., aorto-aortic and aorto-visceral. With involvement of the renal artery an aorto-aortic and if feasible aorto-renal bypass is desirable. Aorto-renal bypass is possible when the constriction of the renal artery is at the origin of the artery or environs. If there are multiple stenoses or if a long segment of the renal artery is involved, nephrectomy has to be considered. The results of nephrectomy have been variable.

Summary

Abdominal aortic coarctation with elevated blood pressure in the left leg or both legs is comparatively uncommon. A case is reported in a young girl with hypertension in all four limbs. The suggestive clinical features and excretion pyelography are stressed. The clinical features differentiating thoracic and abdominal coarctation and treatment are brought out. Functional overactivity due to increased blood supply to the adrenals as a possible cause for paroxysmal hypertension is suggested. The superiority of retrograde aortography is stressed.

Addendum

Subsequent to submission of this article, the patient had a thromboendarterectomy and an aorto-aortic bypass. She is now symptom free.

Our thanks are due to the Dean, Madras Medical College and General Hospital, Madras, for permission to publish this report.

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Clinical pathologic conference

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Case history

A 53-year-old Negro seamstress entered the hospital because of syncope.

The patient had been known to have had hypertension and heart disease for many years and for a two or three year period she had taken digitoxin regularly, ending some nine months prior to her entry into the hospital. One year previously, because of abnormal chest x-ray findings, she was given a course of adrenocorticosteroid therapy by her local physician that lasted five months. For several months she had noticed a vague ache along the right costal margin. One month prior to admission she noticed easy fatigability, exertional dyspnea, and ankle edema. A local physician again prescribed digitalis and administered an injection. Thereafter the patient felt better and was able to work until the day of admission. For the several nights preceding entry into the hospital she experienced profuse diaphoresis and some nocturia, but no chest pain or palpitations. On the morning of admission, shortly after arising, she fainted and upon awakening vomited. Because of two more such episodes, she was admitted to the hospital.

On admission, the patient was a well-developed, moderately obese, pale, diaphoretic Negro woman, unable to stand and in some acute respiratory distress. The pupils were round, regular and equal, and reacted to light and accommodation. The sclerae were clear and the extra-ocular movements were full. The fundi were normal. A small amount of blood was noticed on the right side of the nasal septum but the ears, mouth, and pharynx were clear. There was neck vein distention with the head of the bed at a 30 degree angle, but the veins collapsed when the elevation was 60 degrees. The carotid pulsations were full and there were no bruits. There were fine bilateral basilar inspiratory rales and occasional wheezes, but the lung apices were clear. The point of maximum cardiac impulse was 2 cm. to the left of the midclavicular line and there was a diffuse systolic lift over the precordium. A protodiastolic gallop and a Grade 2/6 blowing systolic murmur were audible at the apex. The abdomen was soft, obese, and nontender. The rounded liver edge was palpable 2 cm. below the right costal margin. The extremities were cold and diaphoretic, but free of cyanosis and edema. The uterus was enlarged, firm, and irregular. The deep tendon reflexes were 3+ bilaterally. The neurologic examination was otherwise physiologic.

The temperature was 99.8° F. rectally, the pulse 120 beats per minute and regular, the respirations 40 beats per minute and shallow, and the blood pressure 170/120.

The hemoglobin was 15.5 Gm./100 ml. and hematocrit 48 per cent. The white blood cell count was 13,200 per cubic millimeter with 80 per cent polymorphonuclear leukocytes, 3 bands, 13 lymphocytes, 2 monocytes, 1 eosinophil, and 1 basophil. The red cell morphology was normal and the platelets were adequate on smear. The admission urine had a specific gravity of 1.011 and a pH of 6.5. It gave a 4+ test for albumin but a negative test for glucose. The sediment contained 10 to 20 white blood cells, a rare red blood cell, and a few bacteria and yeasts per high power field, and 0–2 hyaline and 0–2 coarsely granular casts per low power field. Subsequent urinalyses were normal. The sodium was 137 mEq., the potassium 3.9 mEq., the chloride 93 mEq., the CO_2 30.7 mmoles per liter, and the venous pH was 7.42. Arterial gas studies revealed a CO_2 content of 27.7 mmoles per liter, a pH of 7.44, a pO_2 of 84, and a pCO_2 of 43 mm. Hg.

The blood urea nitrogen was 10 mg., the creatinine 0.9 mg., and the blood glucose 144 mg. per 100 ml. The direct and total bilirubin counts were 0.3 and 0.7 mg. per 100 ml., respectively, and the amylase was 40 Russell units. The serum glutamic oxalacetic transaminase (SGOT) was 42 units, the serum glutamic pyruvic transaminase (SGPT) was 38 units, and the serum lactic dehydrogenase (LDH) 668 units. The serum calcium was 8.9, the phosphorus 4.0 mg. per 100 ml., and the alkaline phosphatase 3.5 Bodansky units. The total protein was 7.3 Gm. per 100 ml. with 49.1 per cent albumin, 6.5 per cent α_1-globulin, 12.2 per cent α_2-globulin, 12.2 per cent

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β-globulin, and 19 6 percent γ-globulin. An immunoglobulin assay revealed an IgG of 2,800 mg an IgA of 690 mg and an IgM of 94 mg per 100 ml. Tests for lupus erythematosus (LE) cells and antinuclear antibodies were negative. N merous sputa were negative for acid-fast bacilli and for malignant cells. Skin tests for tuberculosis, histoplasmosis, blastomycosis nd coccidioidomycosis were negative.

The vital capacity w 1 27 L. (predicted 2.43 L.) of which 1 16 L. or 91 per cent were expired in the fir t second The maximum oluntary ventilation (maximal breathing capacity) was 60 L. (77 per cent of predicted), and after bronchodilators it increased t 84 per ent of the predicted alue. The total lung capacity w 2 10 L (predicted 4 11 L.) and the residual volume w 0 76 L. (predicted 1 68 L.) The t of the residual olume t the total lung capacity w 36 per cent (predicted 41 per cent). The helium d lution curve showed some delay in intrapulmonary m xing

Roentgenograms of the chest were interpreted as how g cardiomegaly right diffuse honeycombing, and h lar lymphadenopathy X ray of the upper nd lower ga tro testinal tract nd of the gall bladder were ormal except for a mall hiatus hernia.

The admission elect ocardiogram showed sinus tachycardia t 115 beat per minute. The P R interval wa 0.18. The S-T segments were depressed in Leads I II V L and V through V_6. The T waves were small in ll leads, notched in Leads II and V through V_6, and apparently merged into U waves in these leads. Subsequent tracings showed waxing and waning of the ischemic alter tions, a digitalis effect, suggestion of left ventricular hypertrophy and toward the end complex trial and A-V junctional tachycardias w th A-V dissociation.

The patient was treated with rest, oxygen digoxin, and d uretics and seemed to be somewhat improved. Frequent episodes of tachypnea early in the hospitalization led to the use of anticoagulants. In addition hydration was maintained and theophylline w administered Although the sputum grew only the usual saprophytes, tetracycline was given in divided da ly doses.

Nausea and omiting developed but subsided when digoxin w discontinued and gitalin substituted

The patient persistently produced copious amounts of mucopurulent sputum. On the sixtieth hospital day she piked a temperature of 101 and her white cou t w 14,500 per cubic millimeter A sput m cultur grew out no pathogens except for an occasional Candida species. Ampicillin wa given and the patient s temperature returned to normal in 24 hours.

The patient course was punctuated by several syncopal episodes lasting from several seconds to several minutes, unaccompa ied by incontinence seizure activity or focal neurologic signs. The serum LDH rose a high as 835 units. The spinal fluid was normal. These syncopal episodes tended to occur when the patient shifted position suddenly She awakened from them perfectly oriented nd without neurologic sequelae

On the seventieth hospital day a chest x ray revealed a left lower lobe infiltration. Methicillin and chloramphenicol were given. The following da the patient complained of extreme fatigue The te perature rose to 102° F the pulse was 12 the res rations 50 and the blood pressure 90 60 Wh being examined, the patient pulse suddenly beca unobtainable and she died.

Discussion

DR. LLOYD FERGUSON We have for con sideration this morning a middle-aged Negro woman who died a few short wee after the apparent onset of an illness ma fested principally by tachypnea diffuse pul monary infiltrates a relatively normal ma imal breathing capacity and hypoxemi without hypercarbia Our problem is to find the language with which to characteriz such an illness

Before I discuss what I hope is the basi disease one or two other problems warrant mention In a patient with known hyper tension who presents with dyspnea, pulmo nary râles, distended neck veins, and a pro todiastolic gallop the diagnosis of conge tive failure seems reasonable I think she did have congestive heart failure, but on a different basis than the hypertension, and I doubt that cardiac decompensation wa responsible for her presenting symptoma tology

I am somewhat at a loss to explain thes peculiar syncopal episodes. Several poss bilities come to mind. Could this be a form of Stokes-Adams syncope due to cardia conduction disturbances? The recent re initiation of digitalis and diuretics, the su gestion of hypokalemia on the initial ele trocardiogram and the vomiting that fre quently accompanied these episodes lend credence to the theory that digitalis intox cation may have been responsible for such a disturbance. Moreover the patient wa observed to have several such attacks in the hospital and digitalis toxicity wa documented by the last electrocardiogra What role the hypoxemia may have ha in the precipitation of these attacks is not clear If this were a major facto it would be difficult for me to expla her rapid spontaneous recovery from the episodes. May we see the electrocard grams now?

DR. ALFRED PICK Sixteen electrocard grams were taken on this patient over a period of 3 months and the pertinent one

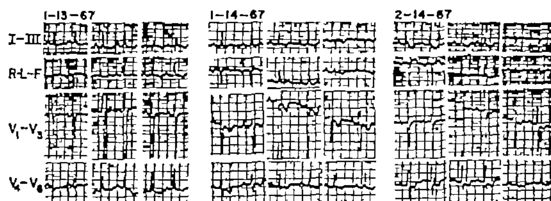


Fig. 1 Three electrocardiograms taken within the first month of the patient confinement t the hospital. See text for details.



Fig. 2 T later electrocardiograms. The right-sided boxed-in part of the lower tracing is enlarged to double size to demonstrate the tw types of P waves. Horizontal bars within the record ndicate the A-V conduction time of ventricular captures. See text.

are illustrated in Figs. 1 and 2 The admission record (Fig 1 on January 13 the day of admission) shows a sinus tachycardia of 111 with a normal P R interval (0 18 sec) and large 1 waves n Lead II and in the right precordial leads, suggesting enlargement of the right atrium The QRS complexes show respiratory variations in the limb leads, especially in Lead III corresponding to a respiratory rate of about 40 established on a long strip (not shown)

The huge, predominant S waves in V and V are consistent with left ventricular hypertrophy However the expected ST T configuration of left ventricular "strain appears to be modified by other factors, most likely hypokalemia of moderate degree, suggested by the broad flat T U combination extending to more than one half of the ventricular cycle. This record therefore, is consistent with hypertensive heart disease probably combined with

chronic lung disease in respiratory distress and electrolyte imbalance.

On January 14 the sinus rate is slower (86) and the P R interval has lengthened to 0 20 sec. P and QRS are unchanged The T waves are no longer broadened and are distinct from smaller U waves, seen best in V_1 and V_2. The S-T is short and depressed merging imperceptibly into inverted T waves in all precordial leads. Thus hypokalemic modifications of a left ventricular hypertrophy pattern have yielded to alterations characteristic of digitalis effects However the marked T inversion in V_1 through V does not fit such a pattern entirely and suggests the possibility of some myocardial changes the nature of which is not evident in the electrocardiogram Ischemic alterations caused by acute hypoxia or some diffuse active inflammatory process have to be considered This assumption is supported by comparison with the next record on February 14 when with a faster sinus rate of 111 and a P R of 0 20 only a typical digitalis configuration of ST T is seen in association with the pattern of left ventricular hypertrophy

In Fig 2 is illustrated a Lead II obtained on March 20 in which these therapeutic digitalis effects are heightened by the addition of a slight P R prolongation to 0 24 sec. while the sinus rate is regular at a rate of 83 beats per minute. The record obtained on April 11 is Lead II of the last tracing on this patient on the day of death and shows an unusual and complex arrhythmia. As seen in the enlarged segment, there are two types of P waves (labelled P_1 and P_2) both regular differing both in rate (107 and 58 respectively) and in shape from the original sinus P waves the slower upright P_2 is narrow and pointed the faster inverted P_1 small and inverted The ventricular complexes are unchanged in shape and occur at a different rate of 115 in regular sequence except for occasional earlier ones that are always linked to a P_1 at a P_1 R interval of 0 28. These premature complexes occur predictably whenever an R P_1 interval measures 0 16 sec

On the basis of all of these measurements the following interpretation becomes possible There are three discrete ectopic and dissociated rhythms. Two pacemakers dominate the atria protected from each other and hence completely independent (atrial parasystole)[1-4] The other dissociation is at the atrioventricular junction and is caused by the acceleration of an A V junctional pacemaker—a nonparoxysmal A V junctional tachycardia[6]—in combination with a complete retrograde block and with only a minor degree of antegrade A V block that permits capture of the ventricles by some impulses of the faster (P_1) atrial pacemaker Thus, the A V dissociation is incomplete.[7]

Acceleration of ectopic atrial or A V junctional impulse formation is a common occurrence in clinical electrocardiography as a manifestation of relative digitalis excess after potassium depletion[8] especially during hypoxic states such as those that occur in chronic lung disease or when myocardial function is compromised by an active or by a residue of a diffuse myocardial process of an inflammatory or ischemic nature Any single one or a combination of these factors may have caused this rare coincidence of a triple cardiac rhythm with double dissociation.

In summary the electrocardiograms in this case permit the following prediction of anatomic findings left ventricular hypertrophy in chronic lung disease right ventricular hypertrophy may be present, but, if so it is obscured by the predominant pathologic changes of the left ventricle. There is also an acute or a healed or chronic myocardial process of undetermined nature. Conceivably the atrial myocardium may also be involved These anatomic findings can then be considered a proper background for digitalis sensitivity as indicated by the unusual functional alterations in the terminal electrocardiograms.

DR. FERGUSON I have no doubt that pulmonary infection was a complicating factor at various times throughout the patient's hospital course but here again, I find it difficult to ascribe the entire clinical picture to this area

The subjective sensation of dyspnea, the hyperventilation manifested primarily by tachypnea rather than hyperpnea, the *diffuse* pulmonary involvement, both clinically and radiographically the reduced arterial oxygen tension, and the normal or slightly decreased arterial CO_2 tension are strong evidence in favor of a primary dif-

fusion defect. I find it useful to remind myself from time to time that CO_2 is twenty times as diffusible as oxygen and that interference with the diffusion of oxygen between the alveolar air and the pulmonary capillaries can exist as a result of thickening of the alveolar walls, even though the CO_2 tension is low. I think this combination serves to distinguish diffusion problems from alveolar hypoventilation in which there is also arterial hypoxemia, but in which one would expect to find hypercarbia as well.

The possibility of a shunt deserves consideration and it would have been comforting to see the arterial pO_2 rise to normal after breathing of 100 per cent oxygen, thus eliminating a shunt as the explanation.

For reasons that are only partially clear to me, it is no longer fashionable to speak of alveolar capillary block. One hears more nowadays about ventilation perfusion discrepancies. Fortunately for the uninitiated, including me, the differential diagnosis of ventilation perfusion discrepancies in 1967 is virtually identical to that of the alveolar capillary block of a decade ago. The absence of cyanosis disturbs me in connection with this characterization and, noting that the patient was a Negro, I wonder to what extent melanin might have interfered with the detection of cyanosis. By this time of year the interns will all have learned to inspect the soles of the feet and the under surface of the tongue in such a case. I think then that the clinical, radiologic, and physiologic features of this case define the syndrome of alveolar capillary block and our problem now is to search for clues that would allow a specific etiologic diagnosis. I will make my excuses early and state that this process of determining the etiology may be quite difficult and that pulmonary biopsy may be helpful or even necessary in some instances.

Perhaps this would be a convenient time to ask for help from the radiologist, but the rules of the game require that I give some hint of my own thinking before the radiologist settles the issue. To comply with this regulation I have prepared a list of several questions to which I hope the radiologist will speak.

1. Would the picture be compatible with either widespread bacterial infection or multiple pulmonary emboli?
2. Would it be compatible with either the Hamman-Rich syndrome or scleroderma?
3. Would idiopathic pulmonary hemosiderosis give this x-ray appearance?
4. Is there any suggestion of sarcoidosis?
5. Could this be the picture of lymphatic spread of carcinoma?

DR. BERTRAM LEVIN: The first film we have on this patient was taken two days after admission (Fig. 3); it is a bedside film, frontal view, with the patient upright. There is diffuse honeycombing with both lower lung fields much more extensively involved than the upper lung fields. The heart appears to be somewhat enlarged but this may be an artifact due to the bedside technique of radiography. Certainly there is no massive cardiomegaly, nor is there any evidence of pleural effusion or lymphadenopathy. The next film, eight days later, is also a bedside film and there is no apparent difference except that there now appears to be a left pleural effusion sufficient to obscure that costophrenic angle. The first chest film that was made in the x-ray de-



Fig. 3. Bedside chest film 2 days after admission. There is "honeycomb" pattern present in both lung bases and present to lesser degree in both upper lung fields.



Fig 4 Chest film three weeks later The honeycombing is more evident Bilateral hilar lymph node enlargement is now apparent

partment was taken three weeks after admission (Fig 4) This shows extensive honeycombing and in addition there is bilateral hilar lymphadenopathy There is visibility of the bronchial tree noted through the heart shadow in the left lower lobe There is no evidence of pleural effusion The honeycombing is probably evidence of interstitial fibrosis. The visible bronchial tree reflects an alveolar disease (pneumonia) In all likelihood judging from the extent of involvement, the fibrosis is certainly predominant and whether the basal pneumonia is coexistent or a complication I cannot assess.

The last film taken on April 10 87 days after admission and one day before death shows no alteration except possibly for some enlarging of the heart. I say possibly since the diaphragm is somewhat higher than previously and the heart may be lying more transversely rather than being truly larger Thus, to summarize it would appear that there is a diffuse interstitial pulmonary fibrosis with a superimposed left lower lobe pneumonia.

To answer your questions Dr Ferguson The honeycombing is not the picture of widespread bacterial pneumonia. Of course, there could well be secondary bacterial infection and this may well account for the basal air bronchogram. Multiple pulmonary emboli do not appear as honeycombing on the chest roentgenogram nor is there the pleural effusion that one so often sees with pulmonary infarction.

The picture is indeed compatible with the Hamman Rich syndrome. In this disease, the pulmonary infiltration may have a nodular miliary or honeycomb appearance. With the first mentioned appearance there are many possibilities that enter into the differential diagnosis with the honeycomb appearance there are fewer entities to consider Lymphadenopathy may be seen in the Hamman Rich syndrome as can pleural effusion. I would like to see greater prominence of the pulmonary artery segment with such marked involvement of the lung by an interstitial fibrosis The fact that the cardiac configuration is not diagnostic or characteristic of right ventricular hypertrophy does not dissuade me from the diagnosis of diffuse interstitial fibrosis.

Though scleroderma is a fibrotic disease in the lung there is generally less involvement of the upper lobes than one sees in this patient and there is generally more linear fibrosis than in this case Remember also that the examination of the colon and upper gastrointestinal tract shows no evidence of abnormality I realize however that only a small proportion of persons with scleroderma show abnormal gastrointestinal findings. Certainly this patient does not

On the roentgenograms, idiopathic pulmonary hemosiderosis presents a diffuse nodular configuration rather than honeycombing I do not believe that lymphadenopathy is seen in this disease No, I would not consider idiopathic pulmonary hemosiderosis.

Based on the picture alone sarcoidosis may be diagnosed The interstitial lung disease and the lymphadenopathy are all characteristic of sarcoidosis and from the roentgenographic appearance in this case sarcoidosis is certainly a good possibility However on one of the earlier films there is some left pleural effusion Pleural sarcoidosis is extremely rare but of course this does not preclude the possibility of a



Fig. 5 An overall view of the heart and lungs. The lungs are overexpanded and tend to cover the heart.

person with sarcoidosis having an associated nonsarcoid pleural disease or effusion due to heart failure.

The findings are not good for the lymphatic spread of cancer. First, the honeycomb appearance is not accompanied by any dilation of the interlobular septa (Kerley B lines) and there has been no recognizable change over the two months observation. If the changes noted on the very first films are due to metastatic cancer, I would have expected that by two months there would be marked progression.

Thus, the roentgenographic appearance would favor sarcoidosis or idiopathic pulmonary fibrosis.

DR. LLOYD FERGUSON. The complete list of disease entities that can give rise to the syndrome of alveolar capillary block is quite long and I shall not attempt to recite it in its entirety. Many of the conditions can be summarily dismissed in the present instance on the basis of the occupational and exposure history. I will assume, for instance, that phosgene and sulfur dioxide are not legitimate considerations and that the patient did not have post-irradiation fibrosis. Similarly, there is no information that the patient ever worked in the fluorescent light bulb industry, nor was she ever employed in a foundry, so that I think berylliosis and silicosis can be safely excluded. Pulmonary edema can lead to a decrease in diffusing capacity, but such a physiologic abnormality is not seen in all cases of pulmonary edema, nor does the decrease in the diffusing capacity correlate well with the extent of the edema. I think that the rather static nature of the roentgen changes is evidence against this as the primary dis-



Fig 6 The external surface of the right lung A hobnail appearance of the lower and middle lobes is evident

ease here as I find it hard to believe that pulmonary edema on the basis of hypertensive heart disease would not have either resolved at least partially or resulted in an earlier death. If multiple pulmonary emboli were occurring at a rate sufficient to account for this x-ray picture, I would have expected the patient to have had at some point, pleuritic chest pain hemoptysis or a substantial rise in the serum LDH level. There was no evidence of peripheral venous disease and the patient was up and about right up to the time of her hospitalization. Moreover over the period of observation I would have expected more dramatic changes in the x-ray picture—that is, once again, I think the relatively static nature of the x-ray changes is a point against this diagnosis

Pulmonary involvement with scleroderma can produce at least the physiologic aberrations observed here but there is no mention of the skin and esophageal changes that would provide confirmatory evidence. Similar reasoning applies to the pulmonary changes of other so-called collagen diseases, in particular dermatomyositis and rheumatoid arthritis

Lymphatic spread of carcinoma is possible but in the absence of profound cachexia and any obvious primary I cannot rule this diagnosis.

I suppose one should mention pulmonary alveolar proteinosis, but the x-ray is not typical and even in the presence of typical x-ray findings, the chest physical examination is often normal in that condition

Idiopathic pulmonary hemosiderosis



Fig. 7 Cross section of the right lung following inflation There is honeycombing of the lower lobe and emphysema of the upper lobe.

curs primarily in youngsters under 16 and males predominate in the ratio of 2 1 This patient did not exhibit the severe hemoptysis, the digital clubbing and the hepatosplenomegaly that would make one comfortable with that diagnosis. Furthermore, idiopathic pulmonary hemosiderosis is episodic in nature, and here we seem to be dealing with a relentlessly and rapidly progressive malady

Sarcoidosis, by its very nature, is a diagnosis of exclusion but the process of excluding it from diagnostic consideration can be quite difficult. There are none of the peripheral manifestation of this granulomatous process. While we are in the area of the granulomas, I shall assume that the negative skin tests and the numerous negative cultures for *Mycobacterium tuberculosis* are strong points against miliary granulomatosis of infectious origin in particular tuberculosis and histoplasmosis.

In 1933 and again in 1944[10] Hamman and Rich reported four patients with a peculiar form of pneumonia characterized by progressive fibrosis of both lungs, progressive hypoxia, right ventricular failure and death within a few weeks to one year By 1957 the concept had been mongrelized to include more chronic forms of interstitial fibrosis and including these, Rubin and Lubliner[11] were able to cull more than 60 cases from the literature. Hypergammaglobulinemia has been described in certain instances. The clinical and roentgenographic picture and the physiologic abnor



Fig 8 A connective tissue stain (Verhoeff Gieson) of one of the lower lobes showing thickening of the septae, formation of cysts, and arteriosclerosis. A modest degree of fibrosis is evident.



Fig 9 A silver stain showing the dense proliferation of the reticulin fibers in a similar area.

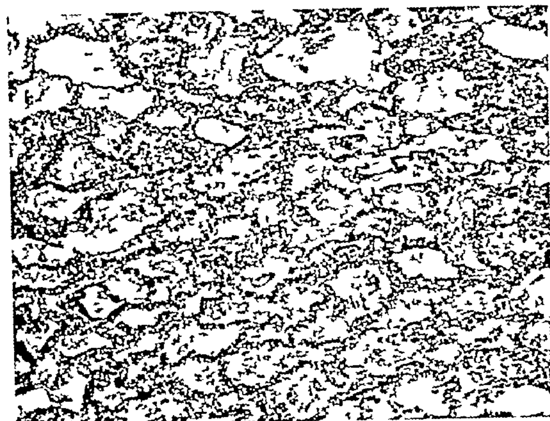


Fig. 10 A low power view of section from one of the upper lobes where the disease is still active. There are areas of edema, infiltration with pneumocytes, and hyaline membranes.

malities in the present cases are consistent with this diagnosis.

Although the electrocardiograms were not diagnostic of right ventricular hypertrophy enlargement of the right ventricle may have been overshadowed. I think I shall settle then on a diagnosis of diffuse interstitial pneumonitis (the Hamman Rich syndrome in its classic form) with cor pulmonale and right ventricular failure

DR. ANN POLLAK It is a pleasure to be able to confirm every diagnosis that the consultants have suggested

The body was that of a well developed fat Negro woman appearing to be the stated age of 53 years measuring 151 centimeters in length and weighing 69 kilograms.

The main features of interest resided in the chest. The right pleural cavity contained 100 ml. of straw-colored fluid and the left 200 ml. of similar fluid. Moderately numerous fibrous adhesions were found chiefly involving the right upper lobe. The right lung weighed 830 grams and the left, 650 Both lungs were firm On section both upper lobes revealed numerous air filled cysts, most numerous in the lower lobes, apparently bronchiectatic in origin surrounded by bands of translucent greyish white tissue. There were numerous firm, translucent grey nodules present scattered through the parenchyma. In addition a large amount of frothy fluid could be expressed from the upper lobes

Microscopy revealed a variety of interesting lesions, all suggestive of the usual form of interstitial fibrosis of the lung The alveolar walls were thickened As usual this thickening consisted of a marked proliferation of reticulin a moderate increase in elastic fibers and only a modest multiplication of collagen bundles. Rare smooth muscle fibers were present. Many of the alveolar septa showed clubbed ends Numerous cavities of varying sizes were present, some obviously made up of confluent



Fig 11 The right ventricle of the heart showing both hypertrophy and dilatation.

alveoli others much larger and of indeterminate origin. In many areas, there was evidence that the process was still active as the alveoli were lined by hyaline membranes. In these areas, the alveoli were filled with granular debris or a fibrin network in which numerous inflammatory cells were embedded. The infiltrate consisted primarily of granular pneumocytes, a moderate number of polymorphonuclear leukocytes, and occasional giant cells. The thickened alveolar walls presented a similar inflammatory infiltrate here however a few eosinophiles were also found

As suggested this woman had evidence of an acute infection superimposed on her underlying disease several of the cavities were filled with pus with patches of acute bronchopneumonia surrounding these abscesses.

As might be expected the lungs showed severe pulmonary arterial and especially arteriolar sclerosis, particularly in the scarred areas. There was even more noticeable distention of the pulmonary veins and the bronchial veins. Prolonged search revealed only a single sclerotic bronchial artery however

The hilar lymph nodes were moderately to severely enlarged. They showed anthracosis and reactive hyperplasia, but no granulomas.

The heart, weighing 360 grams, showed biventricular hypertrophy and bilateral hypertrophy and dilatation with a striking degree of right ventricular predominance. The left ventricle measured 1.5 centimeters in thickness, while the right measured up to 0 8 centimeter A marked degree of coronary atherosclerosis was present, chiefly involving the anterior descending branch of the left coronary artery and a moderately severe degree of coronary arteriolar sclerosis, more marked in the left ventricle. Microscopically focal fibrosis was present in the left ventricle In addition, there were some scattered foci of interstitial myocarditis present This lesion was more marked in the right ventricle than in the left. Focal interstitial myocarditis is an uncommon lesion and one that is sometimes hard to explain. In this case, I assume that it represented a spread from the acute infection in her lungs. I have no doubt that it contributed to the death in this case. Unfortunately the atria were not examined histologically

Generalized atherosclerosis was pres-

particularly involving the right internal carotid artery where it was the obvious cause of her syncopal episodes. Small paraventricular infarcts were present in the medulla.

This case, then, represents an example of interstitial fibrosis of the lung. This lesion has been commonly miscalled the Hamman-Rich syndrome, a term properly applied only to the rapidly developing form of this disease. To avoid this misnomer Liebow coined the term *usual interstitial pneumonia* (UIP) for this pathologic entity. In a recent publication Liebow[*] has brilliantly summarized our current knowledge of this disease. Briefly UIP follows a wide variety of insults to the lung: viral pneumonia, oxygen poisoning, and auto-immune diseases are examples. Occasional hereditary cases, particularly in association with neurofibromatosis, have been described. In the present case, the etiology is unknown.

The lungs also showed extensive arterial and arteriolar sclerosis of the pulmonary circulation as might be expected in a patient with such marked destruction of the lung parenchyma. Nevertheless, there was very little evidence of the increased collateral circulation that frequently occurs in such cases[*] since prolonged search revealed only a single sclerotic bronchial artery and no plexiform lesions at all.

The final diagnosis, then, is (1) usual interstitial pneumonia (UIP) with fibrosis and honeycombing (2) severe pulmonary arterial and arteriolar sclerosis (3) focal bronchopneumonia (4) cor pulmonale (5) coronary atherosclerosis, severe, with focal myocardial fibrosis (6) focal acute myocarditis (7) generalized atherosclerosis particularly involving the right internal carotid artery (8) paraventricular infarcts of the medulla oblongata (9) exogenous obesity

DR. DAVID RADNER How does this lesion differ from desquamative interstitial pneumonia (DIP)?

DR. ANN POLLAK Dr Liebow has described *desquamative interstitial pneumonia* as another form of interstitial pneumonia. The two lesions are quite similar and DIP may also end up with honeycombing. Furthermore it is true that occasional alveoli in this case show extensive desquamation of pneumocytes. The difference is one of degree. In DIP the predominant lesion is one of extensive intra-alveolar desquamation of pneumocytes without the necrosis and fatty change seen in alveolar proteinosis. The alveolar septa are almost or entirely normal with little or no interstitial inflammatory infiltrate. If treatment is started early there is a good response to steroid therapy. UIP on the other hand is primarily an interstitial disease with extensive thickening and infiltration of the alveolar septa and trivial and inconstant evidence of intra-alveolar desquamation and proliferation. Clinically the response to steroid therapy is usually unimpressive. It is the latter picture that predominates in this case.

UNIDENTIFIED PHYSICIAN Dr Pollak, what do you think is the cause in this case—is this an auto-immune disease

DR. ANN POLLAK We do not know the cause in this case as we do not know the cause in the majority of these cases. Recently much attention has been paid to a possible auto-immune etiology. Mackay and Ritchie[1] and Gottlieb and associates[*] have both recently reviewed the literature and reported their own observations. Approximately one quarter of these cases are associated with classical rheumatoid arthritis and another quarter show serologic evidence of auto-immune antibodies. The remaining half however show no such evidence despite quite thorough and sophisticated searches for them and no other cause has been found either

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Fundamentals of clinical cardiology

The nature of intercoronary arterial flow in the normal heart

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Anatomists after injecting a single coronary artery with liquid gelatin and observing its rapid appearance in adjacent coronary arteries have concluded that the coronary tree anastomoses freely upon the surface of the heart.[1] Clinicians on the other hand, observing the sequelae of sudden coronary occlusion, have inferred that intercoronary anastomoses are not normally present and that the coronary arteries function as strict end-arteries. The following report addresses itself to this controversial subject.

Experimental work in this area has produced many contradictory findings and attests to the peculiar nature of normal coronary anatomy. Schlesinger and Zoll,[-11] after radiographic examination of postmortem human hearts in which Schlesinger mass was injected, concluded that only 9 per cent of normal hearts had intercoronary anastomoses of 40 microns or greater. Similarly, Pitt,[12] after injecting wax spheres of 35 to 90 microns in diameter into one coronary artery and attempting their recovery from the opposite coronary artery, concluded that only 6 per cent of normal human hearts had significant intercoronary anastomoses. Conversely, Baroldi and associates, using cast corrosion, described many intercoronary communications of 20 to 350 microns in diameter and Prinzmetal and co-workers, after injecting postmortem human hearts with radioactive red blood cells and glass microspheres, concluded that numerous communications from 70 to 180 microns exist between branches of normal coronary arteries.

Despite these differences of opinion there is more or less general agreement about intercoronary communications on two points. First, in the presence of gradual coronary occlusion, epicardial collaterals of arteriolar size and greater develop, and second, backflow through an acutely occluded and cannulated coronary artery in the intact, normal opened-chest dog occurs. Backflow has been shown by Kattus and Gregg[11] to be directly proportional to systemic pressure and unaffected by heart rate or vasodilatation

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Gregg and Rewald[1] have also demonstrated that backflow blood in dogs with rich collaterals produced by chronic coronary occlusion is arterial and derived predominantly from adjacent coronary arteries. What has not been determined however is the source of blood entering the territory of an acutely occluded normal coronary artery

The following experiment was devised to determine if the normal coronary artery is an end artery or an artery which has no communications with other arteries outside its distribution and therefore, when occluded receives blood by retrograde flow through the cardiac veins coronary sinus or from the ventricular lumen or if it is a communicating artery and receives blood from adjacent coronary arteries and if so the nature of these communications

Materials and methods

Five groups of adult mongrel dogs weighing 20 to 25 kilograms were anesthetized with sodium pentobarbital heparinized and maintained on a Harvard respirator to which 4 L per minute of oxygen was added The chests were opened through a median sternotomy and the aorta cannulated by way of the left subclavian artery In Groups 1 through 4 the aortic cannula was connected to a pressure monitor and through plastic tubing and a three-way stopcock to a No. 14 Bafalo needle which was inserted into the circumflex coronary artery and tied in place (Fig 1) Perfusion of the circumflex artery was maintained in this way except during backflow determinations when the aortic cannula was turned off and the backflow was allowed to egress through a side tube into a graduated cylinder All backflow determinations were made during each animal's normal resting systemic pressure which because coronary occlusion lasted for only 30 seconds, usually held without the onset of chamber enlargement

In Group 1 consisting of 10 dogs a tourniquet was passed around the great cardiac vein at the junction of the ascending and transverse limbs. In addition a No 5 Fogarty balloon catheter was placed in the orifice of the coronary sinus. Collections were made for 30 seconds with the

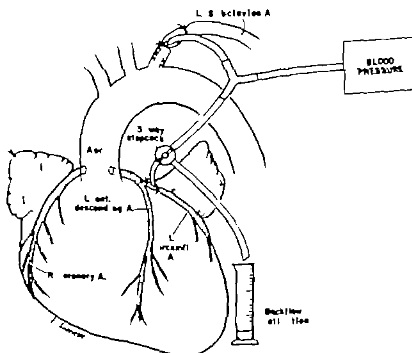


Fig 1 Diagram shows basic preparation used in Groups 1 through 4 The circumflex artery has been ligated and cannulated. Perfusion is maintained through a shunt from the left subclavian artery

coronary sinus and great cardiac vein unoccluded and occluded blood flow was expressed in cubic centimeters per minute.

In Group 2 also consisting of 10 dogs tourniquets were placed around the right coronary artery at its origin and the an tenor descending or left coronary artery so that the septal branch was always included in the ligature. Backflow measurements were again made for 30 seconds with the coronary arteries open and occluded.

In group 3 consisting of 3 dogs, tourni quets were passed around the right and left coronary arteries at their origins. A No 18 plastic cannula was inserted into the left ventricular lumen through its apex and secured with a purse-string suture. The cannula was connected to a roller pump and reservoir of methylene blue. Just after the right and left coronary arteries were occluded a saline solution containing 25 per cent methylene blue was pumped into the left ventricular lumen at 1,600 c.c. per minute until the onset of ventricular fibrillation. During the methy lene blue infusion left ventricular luminal pressure remained equal to systemic pressure, i.e., 110 to 140 mm. Hg Circumflex artery backflow was collected centrifuged and examined optically for the presence of methylene blue.

In Group 4 consisting of 7 dogs, the initial backflow comprising the measured volume of the cannula and the estimated volume of the circumflex artery usually 3 to 5 c.c. was discarded A sample representing blood which had entered the cir cumflex distribution from an outside source was then collected in an airtight syringe and analyzed immediately for pO in a Corning blood gas analyzer and compared with systemic arterial and venous pO_2. The collections required 1½ to 3 minutes of circumflex ischemic time.

Finally in Group 5 consisting of two animals, a Buffalo cannula was inserted into the anterior descending artery and perfusion maintained as in Groups 1 through 4 The circumflex artery was then ligated and methylene blue injected into the anterior descending artery via the Buffalo cannula. Previous experiments from this laboratory demonstrate that intravascular injections of isotonic solu tions of methylene blue stay within the vessels and when methylene blue is in jected interstitially it results in stasis and pooling rather than immediate pickup by the vascular bed Moving pictures were simultaneously taken to establish the time sequence and path of dye spreading across the ventricular myocardium

Results

Systemic blood pressure for all groups averaged 125 mm. Hg and remained con stant during each experiment. The heart rate varied from 100 to 150 and on several occasions fell to 80 after 30 seconds of coronary occlusion. If the heart rate varied by more than 10 beats per minute during the running of consecutive sets of experi ments the individual run was discounted

In Group 1 the measurements listed represent the average of ten runs for each of the 10 animals in this group (Table I) Average backflow with the coronary sinus and great cardiac vein unoccluded was 5 16 c.c. per minute and averaged 2.2 to 11 0 c.c per minute, and with occlusion the average backflow was 5.30 c.c. per minute and averaged 1 4 to 11 0 c.c. per minute.

In Group 2 the measurements listed also represent the average of ten runs for each of the animals used (Table I) Circumflex artery backflow with the right and left coronary arteries unoccluded averaged 5 40 c.c. per minute with a range of 1 9 to 13.2 c.c. per minute, and after occlusion averaged 1 68 c.c. per minute with a range of 1 04 to 3.34 c.c per minute

In Group 3 one running of the experi ment was performed with each animal Centrifuged samples of backflow blood contained no methylene blue in the super natant.

In Group 4 the average systemic arterial pO value (Table II) was 138 mm. Hg with a range of 75 to 270 mm. Hg while the average systemic venous pO was 28 mm Hg with a range of 15 to 39 mm Hg Circumflex artery backflow pO_2 averaged 107 mm Hg with a range of 54 to 20 mm Hg and was lower than systemic pO in all instances.

Photographic studies in Group 5 showed that methylene blue moved across the myocardium into the area of the circumflex artery distribution as a progressively ad

Table I Volume of circumflex artery backflow in Group 1 and 2 hearts

Measurements	*Systemic blood pressure (mm. Hg)*	*Circumflex artery backflow (c.c./min.)*
Group 1		
Coronary sinus and great cardiac vein unoccluded	125	5 16
Range	120–140	2 2–11 0
Coronary sinus and great cardiac vein occluded	125	5 30
Range	120–140	1 4–11 [illegible]
Group 2		
Right and left coronary arteries unoccluded	125	5 4
Range	120–140	1 9–11 2
Right and left coronary arteries occluded	125	1 68
Range	120–140	1 04–3 3[illegible]

Table II pO_2 values of Group 4 hearts

Measurements	*pO_2 (mm. Hg)*
Systemic arterial	138
Range	75–270
Systemic venous	28
Range	15–39
Circumflex backflow	107
Range	54 220

vancing front and did not appear in the circumflex artery until the front had reached its distal branches

Conclusions

It would appear that the transport of blood into an area of coronary occlusion is not related to retrograde flow in the venous side of the circulation since occluding the great cardiac vein and coronary sinus caused little change in backflow Also pO_2 values of backflow blood demonstrate that it is of arterial quality rather that venous. Gregg and Rewald have shown however that occlusion of the coronary sinus for longer periods of time will increase coronary artery backflow They report backflows of venous blood of 39 c.c. per minute from the anterior descending artery 10 to 30 minutes after clamping It has been our observation that after 5 minutes of coronary artery clamping the heart begins to dilate and coronary backflow goes up considerably as the capillary bed between coronary arteries expands and can therefore facilitate the transport of blood However if coronary clamping is limited to 30 seconds, dilatation does not occur and occlusion of the coronary sinus and great cardiac veins has no effect on backflow

Since methylene blue was not found in Group 3 backflow samples, it was concluded that absorption from the cardiac chambers did not occur However the amount of methylene blue used was small the technique for determining its presence in backflow blood was inexact and much of it may have been jetted through the aortic valve without having a chance to be absorbed. Communications between the coronary arteries and the ventricular lumens exist[12] and drainage through these channels is known to occur in the isolated heart preparation.[1] Although it was not demonstrated in this preparation these channels may well play an important role as an additional blood supply to the heart in the presence of severe coronary artery disease.

Since circumflex backflow fell by 80 per cent with occlusion of the right and anterior descending coronary arteries, it must be concluded that most of the blood entering the area of occlusion is derived from adjacent coronary arteries, while the remaining 20 per cent may represent blood already present in the myocardium which is squeezed out by cardiac action.

Photographic studies in Group 3 provide helpful information in understanding the sequence and pathways of the intraarterial transport of blood. In Fig 2,a methylene blue can be seen in the anterior descending artery just after injection. The myocard

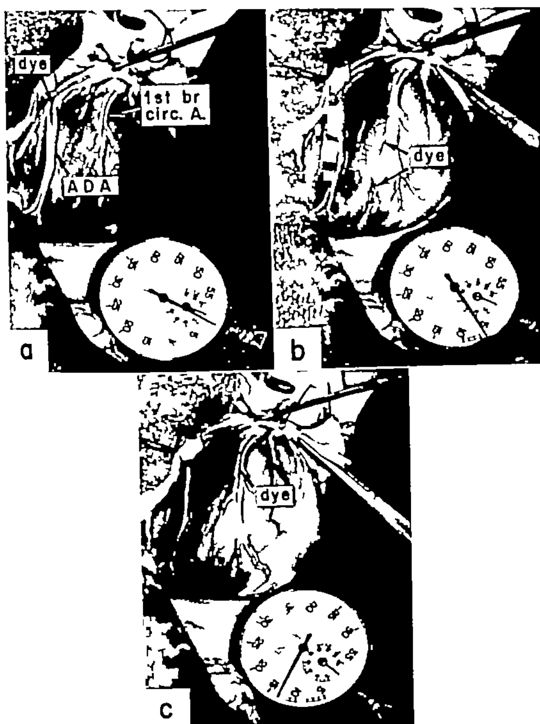


Fig. 2. *a* Arrow points to methylene blue in anterior descending artery of an in situ, beating heart shortly after injection. *b* Arrow points to methylene blue in distal radical of first major circumflex branch 5 seconds after injection. T... seconds after injection, the circumflex is filled with methylene blue

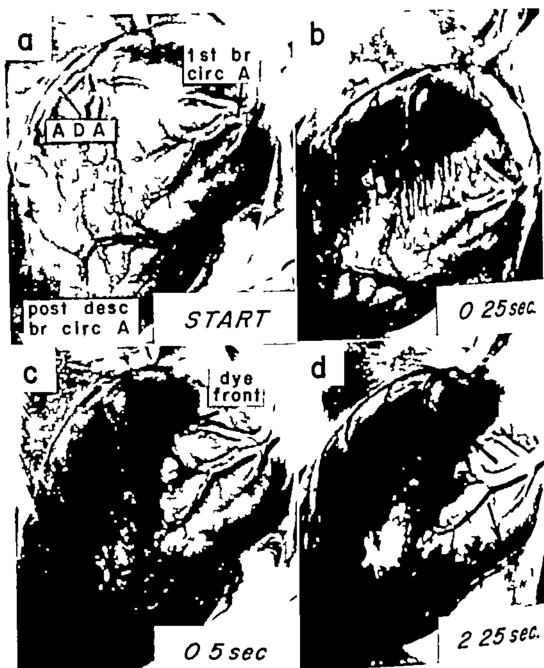


Fig 3 *b c* and *d* The picture is of an in situ beating heart viewed from the apex, so that the anterior descending/posterior descending branch of the circumflex and first major branch of the circumflex artery can be seen. Note that fairly wide margin of myocardium separates the anterior descending artery from the first circumflex branch while narrow margin separates the anterior descending artery from the posterior descending branch of the circumflex at the apex of the heart. *b* Discoloration of myocardium can be seen 0.25 seconds after injection as distribution of anterior descending artery is filled with dye Front of dye advances to the boundaries of anterior descending artery distribution over the next 0.25 second *d* For the next 1.75 seconds the progression of dye stops, but by 2.25 seconds after injection the front has advanced to the distal end of the posterior descending artery which begins to fill and in turn start perfusing its distribution as noted by the appearance of dye around its small branches.

supplied by the anterior descending artery is filled immediately with contrast material but not until 5 seconds after injection (Fig 2 *b*) does dye begin to enter a distal radical of the first major branch of the circumflex artery and not until 12 seconds (Fig 2 *c*) is sufficient methylene blue entering this branch to significantly discolor it.

In Fig 3 *a* which is a different heart, it will be noted that distal radicals of the anterior descending artery are in close

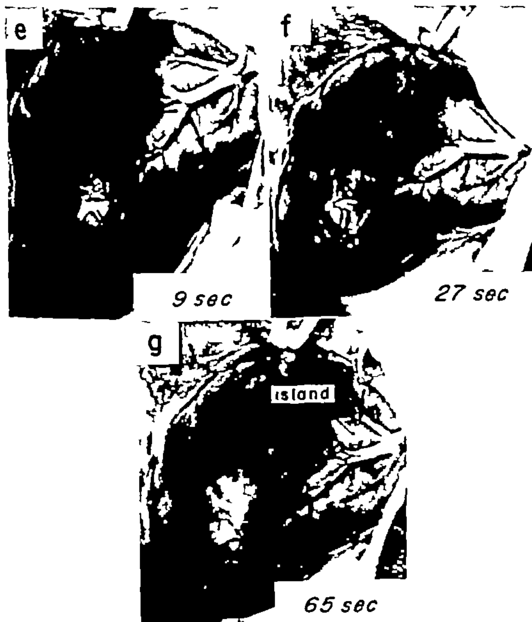


Fig 3 *f* and *g* and *f* Nine nd 27 seconds after jection, the front of dy progresses towards the first circumflex branch. *g* Sixty-fi seconds after injection, the distal radicals of the first circumflex branch ha been reached. Note that as filling occurs, fronts of d appear around its branches and begin t mov outward so that only small islands of myocardium between be branches remain to be perfused.

proximity to distal radicals of the posterior descending branch of the circumflex artery while the first branch of the circumflex artery is separated from its neighboring arteries by a somewhat wider margin of myocardium One fourth second after methylene blue is injected the area of myocardium supplied by the anterior descending artery has been colored (Fig 3 *b*) Over the next 0 25 seconds dye advances to the distal reaches of the anterior descending artery (Fig 3 *c*) and for the next 1 75 seconds, visual progression of dye stops. Then in Fig 3 *d* 2 25 seconds after injection dye begins to appear in the myocardium around the branches of the posterior descending artery and in Fig 3 *e* 9 seconds after injection a second front becomes obvious as more and more dye enters the posterior descending artery In Fig 3 *f* 27 seconds after injection both fronts are advancing on the first branch of the circumflex artery but as yet methylene blue has not filled this branch as demonstrated by the fact that a front of dye has not appeared at its borders. Finally in Fig 3 *g* 65 seconds after injection the two fronts have reached the first branch s distal radicals The branch then fills and starts its own front moving outward so that only small islands of myocardium between arterial branches remain unfilled with methylene blue This sequence demonstrates that blood which has entered a patent coronary artery must first transverse the myocardium before the filling of an adjacent occluded artery can occur and also the closer an occluded artery is to an open artery the more rapidly filling will take place

The type of vessel which provides intercoronary communication in the normal heart can of course only be inferred from this experiment Naturally methylene blue or blood being transported from an occluded to an unoccluded coronary artery must be carried through vessels traversing laterally in the myocardium This includes arterial-size epicardial vessels, subendocardial vessels of 50 to 500 microns in size and capillaries in the substance of the myocardium

While transport through surface or epicardial collaterals may occur the amount is probably not great since contrast material does not appear immediately in the occluded artery and because the pO_2 of backflow blood is not identical to systemic arterial blood

Laterally running subendocardial vessels, termed the subendocardial plexus have been described by Fulton[3] and Estes and associates.[4] The Estes group estimated their size to be 50 to 500 microns and has demonstrated that they communicate with the epicardial coronary arteries through perpendicular vessels in the myocardium. It is certainly conceivable that blood may enter the subendocardial plexus through the communicating vessels of the unoccluded artery traverse laterally enter the occluded arteries communicating vessels and thereby be filled from the subendocardial surface of the heart. It will be noticed from the photographs, however that the occluded branch does not fill until the front of dye advancing across the myocardium has reached its distal epicardial radicals. Therefore, if transport occurs through the subendocardial plexus it must occur simultaneously with or just ahead of transport through the substance of the myocardium

Experimental evidence to date indicates that vessels traversing laterally in the substance of the myocardium are predominantly of capillary size while vessels of 50 to 1 500 microns in diameter are almost uniformly perpendicular Myocardial sinusoids have been described but their course has not been charted Histologically capillaries have been observed by Reynolds and associates[10] and Wearn[11] to run parallel with muscle cells Since the myocardium is composed of laminations of muscle layers running at different angles but parallel to one another around the heart it can be assumed that capillaries in the territory of one coronary artery communicate with capillaries of an adjacent coronary artery This would explain the slow lateral passage of blood from one area of the myocardium to another as well as the frontal type progression across the myocardium

More difficult to explain however is the high pO_2 of blood collected from the circumflex artery One would expect that after traversing the capillary bed between the unoccluded and occluded coronary

artery blood should be venous rather than arterial. The fact that the pO of backflow blood is persistently lower than arterial blood indicates that some desaturation has occurred but obviously not to the degree of true venous blood. Explanation of this phenomenon is not readily apparent in the literature on myocardial microcirculation which is indeed sparse. It would appear however that either capillary flow is altered in such a way by adjacent coronary clamping that the blood is not desaturated or perhaps that transport may not be occurring primarily in the capillaries but in small precapillary vessels of the subendocardial plexus which in turn fill the capillaries through their connecting vessels.

In conclusion these data indicate that in the canine heart communications between normal coronary arteries exist but are primarily at the precapillary level. Therefore blood entering an acutely occluded coronary artery must first pass through the precapillary vessels, surrounding both the occluded and unoccluded arteries. In the absence of cardiac dilatation, the volume of blood entering an occluded coronary artery in this way is so small that the artery should be considered as a functional end-artery.

Summary

The experiment described was designed to investigate the source of blood entering an acutely occluded normal coronary artery and therefore determine whether a coronary artery behaves as an end artery receiving its blood by retrograde flow through the cardiac veins coronary sinus, or from the ventricular lumen or if it is a communicating artery receiving its blood from adjacent coronary arteries and if so the nature of these communications.

In four groups of anesthetized open chested dogs the volume oxygenation and color of circumflex artery backflow blood was measured in the resting state and after cardiac vein occlusion coronary artery occlusion and after the introduction of methylene blue into the left ventricular lumen. The pathways of intercoronary flow were also studied by injecting a patent coronary artery with methylene blue and filming its transport to an adjacent occluded coronary artery.

The results indicate that blood enters an occluded coronary artery from neighboring patent coronary arteries but that transport occurs predominantly at the capillary or precapillary level.

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Cardiopulmonary resuscitation Part I

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Cardiopulmonary resuscitation (CPR) introduced clinically in 1960 by Kouwenhoven, Jude, and Knickerbocker has become an accepted technique for maintaining ventilation and circulation in patients who otherwise might have died from a respiratory or cardiac arrest. CPR is effective in cardiac or pulmonary arrests produced by many causes including apnea, hypoxia, drug sensitivity or toxicity, electric shock, drowning, anesthesia induction, cardiac catheterization, and acute myocardial infarction. Most large hospitals have a team consisting of a surgeon, internist or cardiologist, anesthesiologist, and nurses who are available for such emergencies. Many cardiopulmonary arrests, however, occur outside a hospital where such medical care is not readily available. Not uncommonly these people were healthy prior to the arrest and represent good candidates for resuscitation. Lay or professional personnel should begin CPR and continue until transportation to a hospital for definitive care is accomplished. This ability to effectively ventilate by mouth-to-mouth breathing and maintain circulation by external cardiac compression requires training and retraining of lay, professional, and ambulance personnel in the techniques of CPR. Initiating resuscitation only begins the major problem of treating cardiopulmonary arrest because the ultimate purpose is restoration of the individual to his prior state of health.

The basic techniques of CPR have been reviewed in recent publications and their detailed coverage is beyond the scope of this report. The aim of this review is to discuss certain salient aspects of CPR, care after resuscitation, results, prognosis, and future developments.

Patient selection in cardiac arrest

Although any person with sudden cessation of respiration or circulation is a potential candidate for resuscitation, it is generally not wise to attempt these procedures in patients with advanced neurologic disease, metastatic carcinoma, intractable heart failure, and other irreversibly advanced diseases. However, complex legal and ethical issues are involved in making decisions in these patients. If the medical status of the patient prior to the arrest is not known, or if the advisability of beginning resuscitation is in doubt, it is best to proceed without hesitation. Age alone cannot be the determining factor since many people past 70 are well, vigorous, and capable of surviving a cardiopulmonary arrest.

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Ventilation

A patent airway is essential for successful resuscitation. Following cardiac arrest and apnea, obstructive collapse of the upper airway often occurs. Many unconscious patients are revived following opening of the air passages by backward tilting of the head, forward displacement of the mandible, and clearing the mouth of foreign material or secretions. If these procedures do not lead to spontaneous breathing, immediate mouth-to-mouth resuscitation will produce adequate ventilation. External cardiac massage alone is inadequate for pulmonary ventilation and may produce atelectasis with pulmonary venoarterial shunting and decreased arterial oxygen tension.

Effective resuscitation occurs only when the brain and myocardium are adequately oxygenated. Myocardial hypoxia may initiate ventricular fibrillation or produce cardiac standstill, while profound anoxia for 1 to 20 minutes can lead to irreparable cardiac damage and cellular death. During anoxia the myocardium utilizes anaerobic metabolism for energy production, but adequate metabolic function of the brain is dependent upon aerobic glycolysis. Only four to six minutes of oxygen deprivation produces severe degeneration of nervous tissue with survival rare. Inadequate ventilation also produces hypercapnia, respiratory acidosis, and other metabolic changes which lead to a greater susceptibility to cardiac arrhythmias.

Artificial oral or oropharyngeal adjuncts are not required for effective mouth-to-mouth resuscitation. Simple tubes with a bite block can aid when a bag and mask (Ambu, Aeroflater, and others) are used by professional personnel. A bag and mask should be available in doctors' offices as well as every hospital ward, emergency room, clinic, and other areas where an arrest might occur.

Although mouth-to-mouth breathing and bag-mask resuscitation produce similar airway pressure tracings, the latter is preferable because increased oxygen concentrations can be added at the intake valve and the opportunity for transmission of infection is decreased. In addition, avoidance of direct patient contact is more acceptable to the resuscitator. A foreign body should be suspected if the lungs cannot be inflated following proper positioning and cleaning of the mouth. Observations for the return of spontaneous breathing should be made frequently.

Pharyngeal pressures of 15 to 20 cm. of water, needed during mouth-to-mouth or bag and mask resuscitation to ventilate the lungs, may divert air into the stomach. Only gross overdistension, however, interferes with pulmonary ventilation. Experimentally, gastric dilatation produces increased vagal tone and decreased venous return to the heart. Marked gastric distension in man initiates a vasovagal effect that may produce bradycardia, sinus arrest, or cardiac standstill. Lesser degrees of gastric dilatation may impair cardiovascular function in seriously ill patients, particularly those with hypovolemia, hypotension, or bradycardia. Epigastric pressure can force air out of the stomach, but may cause regurgitation of gastric secretions leading to a blocked airway and possible aspiration. Using a gastric tube with suction is the preferable therapy for relief of gastric distension.

If adequate ventilation does not occur during mouth-to-mouth or bag and mask resuscitation, or if spontaneous respirations do not occur after a brief period, tracheal intubation should be performed. This procedure must be done in a hospital by specialized personnel. Intubation is advantageous because it decreases dead space, prevents regurgitation of stomach contents, and permits easier removal of tracheobronchial secretions. With cuff inflation, positive pressure-cycled ventilation can be instituted with minimal air leak and fairly constant resistance and compliance. During attempts at tracheal intubation artificial ventilation ceases, and if these efforts are prolonged, hypoxia may ensue. The time required for intubation should be brief, with assisted breathing interposed between attempts. Endotracheal intubation can cause laryngeal and mucosal injuries and occlusion of a bronchus. Following mistaken esophageal intubation, a blocked airway, inadequate ventilation, and esophageal trauma may occur. Tracheal stenosis has been noted as a late complication.

Positive-pressure-cycled automat[illegible]

tilators are not recommended when used in conjunction with external cardiac compression. With each external cardiac compression airway pressure increases, causing premature termination of the inflation cycle and insufficient ventilation. However volume-cycled devices or time-cycled ventilators with rapid instantaneous flow rates (greater than 1 L. per second) interposed between compressions, can produce adequate ventilation

During the initial phase of CPR high oxygen concentrations should be administered. There is recent evidence that prolonged administration of high oxygen concentrations causes pulmonary lesions such as intra-alveolar hemorrhage edema, fibrosis, and inhibition of the mucociliary apparatus. The lowest oxygen concentration that maintains an adequate arterial oxygen tension should be administered early in the period after resuscitation

External cardiac compression

When carotid or femoral artery pulsations are absent and heart sounds are inaudible cardiac function and circulation are ineffective. A sharp blow to the midsternum may cause resumption of the heart beat. If unsuccessful external cardiac compression at the lower third of the sternum should be instituted in conjunction with ventilation The main purpose of external cardiac compression is to restore flow of oxygenated blood especially to the nervous system and heart

External cardiac compression performed with the patient lying on a hard surface pushes the heart against the vertebral column and forces blood into the systemic and pulmonary circulatory systems. Upon release the thoracic cage recoils to a normal position producing relatively negative intra-thoracic pressure and enhancing venous return. Effective circulation can be produced whether the heart is asystolic or in ventricular fibrillation During external compression the papillary muscles do not contract, and the mitral and tricuspid valves become incompetent, producing elevated pulmonary and systemic venous pressures The sternal pressure required varies from 80 to 100 lb but depression of the lower third of the sternum 1.5 to 2 in is a better guide to effective compression. External compression at a rate of 60 per minute with equal time (0.5 sec.) spent during compression and release phases is physiologicall optimal because it produces sufficient time for diastolic filling and adequate ventricular emptying In children the rate should be increased and compression performed with one hand With infants and younger children the heart is higher in the thoracic cavity Compression should be made at the midsternum with the second and third fingers at a rate of 100 per minute.

Optimal resuscitation is possible only when ventilation is rhythmically combined with external cardiac compression With two people performing resuscitation an external cardiac compression rate of 60 per minute with a ventilatory rate of 12 per minute can maintain a near normal arterial oxygen saturation and carbon dioxide tension Ventilation is performed after every fifth external compression Other ratios of compression and ventilation may produce hypoxia and a higher arterial carbon dioxide concentration If one person is resuscitating a 15:2 ratio is advisable

Mechanical heart lung resuscitators are advantageous when CPR is required for long periods or when the patient must be moved These units, which may be portable perform similar functions a manual CPR The mean arterial pressure developed and the degree of ventilation achieved are comparable in both methods. With the mechanical units, only one operator is needed and a standard depth of sternal compression can be maintained.

Patients may survive resuscitation only to succumb from complications received during external cardiac compression Strict adherence to proper techniques of sternal compression will decrease trauma to the thoracic cage and underlying organs, but even with proper application rib fractures and costochondral separations are common especially in elderly patients A flail chest pneumothorax hemothorax, subcutaneous emphysema and pulmonary lacerations can occur Bone marrow pulmonary emboli have been reported in 50 per cent of autopsied cases. Hemopericardium with possible cardiac tamponade and aortic rupture are further complications. If the xyphoid process is compressed in error hepatic

lacerations and gastric rupture may ensue.

Internal cardiac massage was employed for cardiac resuscitation prior to the development of the technique of external cardiac compression. Clinical experience has shown that internal massage and external compression are both adequate to sustain life. The time from arrest to onset of resuscitation appears to be more critical than the method used. Few hemodynamic studies of closed compression or open massage have been performed and results are inconsistent. Both methods produce a cardiac output and stroke volume which are approximately 25 to 50 per cent of normal levels. Open as compared to closed cardiac compression produced a higher cardiac output and lower mean circulation time as measured by dye dilution curves. However direct carotid blood flow measurements have been similar in both methods. In closed compression the systolic blood pressure can be maintained at 80 to 110 mm Hg (diastolic 30 to 50 mm Hg) and the arterial oxygen concentration may be higher and the venous return better than in open massage. The central venous pressure is elevated in both methods. Results of hemodynamic studies in dogs comparing closed and open techniques may not be applicable to man. The dog's narrow sternum, long thoracic cage, and relatively mobile heart appear to hinder effective external cardiac compression. Full elucidation of hemodynamic changes in man with internal massage and external compression awaits further investigation.

External cardiac compression is the initial method of choice. The mortality rate has been significantly greater in the open method, perhaps due to delay in therapy and to the added trauma and complications of a thoracotomy in a severely ill patient. Internal massage can be performed only with trained personnel and adequate equipment. It is indicated when the thorax is already opened, when there is intrathoracic pathology requiring thoracotomy (crush injury, cardiac tamponade or tension pneumothorax) or in occasional patients not responding to external methods (marked emphysema).

External cardiac compression causes a mechanical stimulus which produces regular waves on the electrocardiogram. These waves do not represent spontaneous electrical cardiac activity and temporary discontinuation of compression is necessary to evaluate the cardiac rate and rhythm. Frequent palpation of the carotid or femoral arteries, blood pressure determinations, and observations of skin color, pupils and state of consciousness will indicate the effectiveness of CPR.

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Annotations

Posthyperventilation apnea and the criteria of brain damage and death

The criteria of death have assumed immense importance because of the increasing frequency of attempted cardiac resuscitation and the need to salvage organs for transplantation. When life is continued with the use of mechanical respirators, we may, in addition, be asked to decide on the duration of this type of support.

A flat or isoelectric electroencephalographic tracing (Grade V), lack of spontaneous respirations, absence of pupillary and tendon reflexes, and no pulse change from eyeball pressure all for at least one hour have been accepted as criteria of severe permanent brain damage. These criteria present for 12 to 24 hours are thought to *guarantee* irreversible brain damage. Individual criteria, such as the isoelectric electroencephalogram (EEG) are not infallible indications of brain damage. Bird and Plum have described a patient with a flat EEG for at least 23 hours due to barbiturates who recovered with an I.Q. of 122. A similar case has been reported due to encephalitis. A recent experience in the course of cardiac resuscitation illustrates the fallibility of another individual criterion of salvagability, namely the inability to breathe without artificial respiratory support.

The patient was a 52-year-old man admitted for progressive dyspnea, orthopnea, and edema. Digoxin and diuretics produced weight loss and reduction in symptoms. The diagnosis of heart failure of obscure cause with atrial fibrillation was made. It was decided to convert the rhythm to sinus. The patient was maintained on Coumadin. Two days prior to conversion digoxin was discontinued. Quinidine was started one day prior to electrical cardioversion with 330 joules after smaller shocks were unsuccessful. Following conversion, a rare PVC was noted and digoxin withheld. In an electrocardiogram taken five hours after conversion, $T V_{1-4}$ were inverted. Forty-eight hours after conversion, low grade fever and decreased platelets led to discontinuation of quinidine. That same morning the patient was found lying on the floor unconscious and pulseless. An electrocardiogram revealed ventricular fibrillation. The pupils returned to normal size and were responsive to light after resuscitation and defibrillation. Tracheal intubation was performed and the patient placed on a positive pressure respirator (Bennett) with 40 per cent oxygen. Lidocaine, procaine amide, and 89 mEq. of sodium bicarbonate were administered. The patient did not awaken. In the next 18 hours, ventricular fibrillation occurred at least 10 times despite large doses of lidocaine and procaine amide. Twenty-four hours after arrest, he appeared to be hyperventilated on the Bennett respirator (16 cm. of water positive pressure), and had neuromuscular irritability as well as continued attacks of ventricular fibrillation. When the respirator was disconnected, the patient did not breathe during a 40 second period of observation. After this apneic period, the patient was connected to the respirator again, and blood gases were drawn. The patient was found to have respiratory alkalosis with an arterial pH of 7.62, a pCO_2 of 24 mm. Hg, and a pO_2 of 168 mm. Hg. The positive pressure was reduced in steps in the course of an hour until the breathing pattern seemed normal. Neuromuscular irritability stopped, PVC's were fewer, and the episodes of ventricular fibrillation stopped. He was then able to breathe spontaneously though rapidly with small tidal volumes, when the respirator was disconnected. Five and one-half hours later the arterial pH was 7.49 with low positive pressure respiratory support. During the first week after cardioversion, he developed staphylococcal pneumonia and a tracheostomy was performed. He was able to breathe spontaneously and effectively maintain a relatively normal pCO_2, although PO_2 remained low during the episode of pneumonia. Intermittent positive pressure support was used. He showed decerebrate posturings for one day during the first week. He is unable to care for himself but is awake and responds to painful stimuli with epithets. Atrial fibrillation has recurred. Electroencephalographic study of this patient was not possible when he was alkalotic, as he was having frequent attacks of ventricular fibrillation and required monitoring.

One of the accepted criteria of lack of salvagability, namely the inability of the patient to breathe without support, may in fact be due to posthyperventilation apnea in some cases. In one recent study, acute hyperventilation in anesthetized subjects (arterial pH of 7.59) resulted in an average apneic period of 6 minutes and 20 seconds. Eger and Severinghaus also studied posthyperventilation apneic periods and found them to vary from 14 to 20 minutes. In both these studies oxygen-enriched inspiratory mixtures were used. The duration of apnea after hyperventilation is thought to vary with the rate of rise of arterial pCO_2, the initial level of pCO_2 when artificial hyperventilation ceased, and most critically on the depth of central nervous system depression since there are data showing that post

hyperventilation apnea does not occur in subjects who are awake. The rate of oxygenation also affect the duration of apnea; however the carotid body sensitivity to hypoxemia is reduced at low pCO_2 values.

The patient presented here had respiratory alkalosis and a relatively high pO_2, the latter due to a relatively high inspired oxygen tension and hyperventilation. The observed apneic period was undoubtedly posthyperventilation apnea. When respiratory alkalosis was corrected he breathed spontaneously. Certainly the criterion of the inability to breathe the point neously requires the qualification that the apnea is not posthyperventilation in etiology, intensified by a high concentration of inspired oxygen. Episodes of ventricular fibrillation also ceased when the alkalosis was partially corrected. Mild hyperventilation has been used for years to bring out epileptic pattern in the EEG. Severe alkalosis may even be implicated in the production of some EEG abnormalities in comatose patients. Incidentally, ventricular fibrillation one or two days after cardioversion has been noted by others.[10] Quinidine, high energy shocks, and the underlying heart disease may play a role in that arrhythmias.

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Is there an "ideal" cardiac pacing rate?

Increasing the heart rate is one of the most important factors responsible for increasing cardiac output. When the need for a greater cardiac output develops and the ability to vary heart rate is lost, as in complete A-V heart block or fixed-rate cardiac pacing, the patient develops difficulties.

Because permanent electrical pacing of the heart has become so commonplace, there is much discussion about the "ideal" rate at which to set the cardiac pacemaker. These discussions are based upon the assumption that an ideal rate does exist. Excluding the extremes of very rapid and very slow rates, the cardiologist has a reasonably broad range of heart rates from which to select for his patient. Once this rate has been chosen, the patient must learn to live within the limits imposed by his fixed rate and the associated fairly fixed cardiac output. The patient described below illustrates this point very well.

C. S., a 52-year-old paper mill worker, visited his physician in December 1961 because of pain in the left axillary region. An electrocardiogram revealed right bundle branch block. The pain in his left arm subsided and he returned to full activity. He did well until Dec. 1, 1962, when he suddenly became extremely dizzy while training to ... Another episode of near syncope followed strenuous physical exertion. On Dec. 15, 1962, he had syncope and an electrocardiogram revealed intermittent complete A-V heart block. Physical examination revealed blood pressure of 168/80 and ventricular ...

cardia. The heart was slightly enlarged and a systolic murmur was heard best at the aortic area. An x-ray of the chest showed slight cardiomegaly and a dilated aorta with some calcification.

In April, 1963, the patient underwent thoracotomy for the implantation of epicardial electrodes and cardiac pacemaker with the rate fixed at 63 beats per minute. The patient was much improved and had no syncopal episodes. He returned to work as a sample picker. The job consisted of walking long distances to collect samples of paper products. As long as his environment was cool and he did not overextend himself the patient was asymptomatic. However, if the weather became hot and humid, or if he hurried too much, he became extremely weak, almost collapsed, and was unable to continue his work. These symptoms could be relieved by returning to a cool environment or resting.

In May, 1965, the patient again began to experience episodes of dizziness. During one of these episodes his pulse was approximately 20 beats per minute. He entered the hospital so that the contact of one of the epicardial electrodes could be improved and the battery replaced. This time the pacemaker was set at 72 beats per minute. The patient was once again free of dizziness and syncope. With this increase in heart rate he found that he tolerated the hot and humid weather and his long walks much better but he still had to restrict his physical activity. If his activity became too vigorous, especially on hot and humid days, he again became extremely weak and was forced to rest.

Therefore, with the pacemaker rate set at 63 beats per minute the patient did well as long as his body demands for blood did not exceed the capacity of his heart to pump blood. However, during hot and humid weather and/or more vigorous physical exertion, his need for blood was greater and exceeded his fixed cardiac output. He thus experienced extreme weakness and had to rest. Air conditioning was found to be very effective in producing relief from symptoms.

After the patient's pacemaker rate was increased to 72 beats per minute, a great many of his symptoms associated with hot and humid weather and long walks were relieved. Although he could perform a great deal of work without becoming symptomatic, the degree of work was still limited by his fixed cardiac rate.

As illustrated by this patient's clinical course, there is no fixed "ideal" cardiac rate at which to set the cardiac pacemaker. If the rate is set high, as for heavy work, the heart is being "overdriven" at times when demands for cardiac output are low and the heart is overworked when it should be resting. On the other hand, if the rate is too low, minor increases in demand for blood which exceed the fairly fixed cardiac output result in symptoms. It is therefore necessary for the cardiologist to define the situation to his patient clearly and to educate him properly.

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Re-evaluation of septal activation in the human heart

The mechanism of septal activation currently accepted by the majority of clinical electrocardiographers is that of Sodi-Pallares and associates. Studies performed in dogs led these authors to postulate that the first detectable site of ventricular depolarization was the middle part of the left septal surface. Activation of the right septal surface followed that of the left. Although the interventricular septum is depolarized from both sides (Lewis[a]), the over-all process of excitation can be represented by a vector oriented from left-to-right. Intracavitary electrocardiograms recorded from the human heart have corroborated the general sequence of activation predicted from animal experiments. However, in 1959 Scher[a] used a different technique than that of Sodi-Pallares and associates. He also observed that the left side of the septum was depolarized first, but, in addition, noted that activation apparently reached two distinct areas of the left septal mass almost simultaneously. These areas corresponded to the distal portions of the two main subdivisions of the left branch. According to this concept, the normal septal vector oriented anteriorly and to the right is the resultant of two main component vectors. One, directed posteriorly and to the right, represents activation emerging through the inferoposterior division. The other oriented anteriorly and to the left is produced by the electrical impulse as it leaves the anterosuperior division.

The electrocardiographic patterns attributed to block in the anterior-superior and posterior-inferior divisions of the left branch have been clearly outlined by Grant and Dodge, Pryor and Blount, Rosenbaum and associates, and Cohen and co-workers. However, these concepts have been accepted only recently. The main reason for the delayed acceptance of a conduction disturbance which had interested the pioneers in the physiology of bundle branch block as early as 1917[a] was the failure to produce the expected electrocardiographic changes in dogs following section of the corresponding anatomic structures. The work performed by Watt and associates

is interesting because they showed that the predicted axis shifts attributed to block of the anterior-superior or posterior-inferior divisions of the left branch (BSDLB and BIDLB respectively) would occur if primate instead of canine hearts were used for the experiments. Hence, in this instance extrapolation from the dog's heart to that of man proved to be misleading.

At times, one of the most difficult diagnoses in clinical electrocardiography is the distinction between aberration of supraventricular impulses and ventricular extrasystoles in the presence of atrial fibrillation. Several criteria have been used and found to be helpful, but since they are occasionally insufficient, others were proposed. Marriott[14] took advantage of the fact that the most frequent type of aberration is that showing a right bundle branch block morphology. Knowing that right bundle branch block does not alter septal activation, he postulated that orientation of the initial vectors in normally conducted and aberrant beats should be the same. It was therefore disconcerting to observe that only about 50 per cent of proved aberrant beats fulfilled this criteria. Recent work by the Rosenbaum and Cohen groups focused attention on the patterns produced by aberration of spontaneous, or pacemaker induced, premature atrial contractions. Multiple leads and planar vectorcardiograms were recorded so that the spatial sequence of aberrant depolarization could be outlined. These authors noted that although a right bundle branch block pattern was the most frequent type of aberration, it frequently co-existed with a functional BSDLB (and rarely BIDLB). Moreover isolated patterns of BSDLB and BIDLB also occurred. They corroborated the fact that right bundle branch block by itself does not change the general sequence of septal activation. Their most interesting finding was that block in the divisions of the left branch, and not only left *bundle* branch block, could change the direction of the initial vectors. The term initial vector as used here refers to the first 0.02 vector, the septal activation vector.

That both BSDLB and BIDLB are able to change the orientation of the very early QRS vector is an intriguing concept, which can explain several not too well-understood electrocardiographic paradoxes. The reasons for these changes are not known. Rosenbaum and associates have presented an interesting hypothesis. In the studies dealing with aberration of spontaneous atrial extrasystoles they noted that if the electrical position of the heart was such that a q wave was absent in Lead I while being present in II and III, functional BSDLB could change the initial vectors. Abnormal left axis deviation in those instances was associated with q waves in Lead I. R waves were present in II and III. A reverse phenomenon occurred during BIDLB. If q wave was present in Lead I and absent in II and III then when BIDLB occurred, the q wave was absent in Lead I and appeared in II and III. They applied Scher's concepts of septal activation to explain their findings. A basic aspect of their hypothesis is that the orientation of the initial vector is not a function of the main left bundle branch, but is dependent on its divisions. For instance, in the presence of BIDLB the electrical impulse should proceed superiorly through the intact superior division. Here, the first portion of the ventricle to be activated would be the anterosuperior aspects of the left septum and a good portion of the left ventricular wall. The initial vectors will point superiorly, anteriorly, and to the left since they now do not represent a composite vector of septal activation occurring almost simultaneously in two areas of the left septal surface.

In the presence of BSDLB, the electrical impulse proceeds throughout the unaffected inferior division, to the posteroinferior aspects of the septum and the left ventricular wall. Therefore, the initial vectors point inferiorly as well as slightly to the right and posteriorly. Moreover BSDLB also modified the spatial orientation of the initial vectors even when a q wave was present in Lead I and the left chest leads. This change was manifested by variations in the depth of the q wave. In addition, the Rosenbaum group observed the appearance of small q waves in Lead V whenever the latter was obtained above its usual site. The q wave was not due to an anteroseptal infarction but to the reorientation of the early forces.

Although these concepts remain to be proved, they have opened new pathways for future studies of ventricular activation in the human heart.

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Familial dissecting aneurysm complicating Marfan's syndrome

The recent report by Grondin, Steinberg, and Edwards of only the second familial occurrence of necropsy-confirmed dissecting aortic aneurysm in Marfan's syndrome prompts the documentation of similar experience. Here, too, aortic dissection occurred in both mother and son, with the latter also showing fibromyxomatous changes in the mitral valve.

Patient 1 (Ru. B), the mother, had had four uneventful pregnancies. In March, 1960, at the age of 39 after ... one-year history of weakness, malaise, and chest pain, she was found to have ... mediastinal mass by x-ray ... t ... nother hospital. Examination there revealed a thin, pallid woman, weighing 120 pounds and 65 inches in height with long, thin extremities, spindly fingers, high-arched feet, and slight sternal depression. Subluxation of the lens was present. There was ... n apical systolic murmur. The blood pressure was 160/110 mm. Hg. A pulsating aneurysm of the upper abdominal aorta was felt.

The mediastinal mass was believed to be ... dissecting thoracic aortic aneurysm; she was placed on antihypertensive medication. Progressive increase in size of the aneurysm was noted radiographically and in March, 1962, she ... as hospitalized because of increased left chest pain and dysphagia.

Angiography revealed ... aneurysm of the descending thoracic aorta. This was successfully surgically resected from 1 cm. below the left subclavian artery and replaced with ... 7.5 cm. graft, but the patient died postoperatively of cardiac arrest.

At postmortem examination the heart weighed 273 grams and showed only slight hypertrophy of the left ventricular myocardium. The valves were normal as ... ere the pulmonary arteries and coronary arteries. The ascending aorta, innominate, and left common carotid arteries were normal. There was ... saccular dissecting aneurysm of the left subclavian artery starting at its aortic takeoff measuring 2.5 cm. in diameter. Below the distal end of the graft there was a dissecting fusiform aneurysm with ... false channel extending 17.5 cm. downward to the level of the renal arteries. A third 5 cm. long saccular aneurysm was present about 1 cm. ... bove the bifurcation of the common iliac artery. Microscopic examination of the aorta showed cystic medial necrosis.

Patient 2 (R ... B) ... as admitted t ... the hospital in J ... ne 1955 ... t six years of age, for correction of pectus excavatum. Bilateral herniorrhaphy had been performed in infancy and again ... t two ... ears of age. Examination revealed ... tall, thin boy with dolichocephaly, high-arched palate, long hyperextensible finger ... moderately severe pectus excavatum, and inguinal herniae. Later ophthalmologic examination showed myopia and on gonioscopy ... widened anterior chamber angle consistent with the ocular component of Marfan ... syndrome. Examination of the heart ... t this time revealed onl ... fairly loud, rough apical systolic murmur. The blood pressure was 90/55 mm. Hg. Roentgenographic study showed no ... bnormality of the cardiac chambers or great vessels. The electrocardiogram showed an axis of 90 degrees and S-T coving with deep T-w ... inversion in Leads II, III ... V ... V ... V ... and V

He was not seen ... gain until tw ... years later ... t which time the cardiac findings ... ere unchanged. The result of the pectus exca ... tum operation was excellent. The T w ... was no longer inverted in Leads V ... and V. Over the next four years he returned sporadically to the clinic. During this period there w ... no ... hange in his clinical status. He returned in July, 1963, now 14 years of age, ... t which time there was clinical cardiac enlargement with ... left ventricular heave, an early diastolic blow of aortic insufficiency and ... loud systolic blow of mitral insufficiency; the blood pressure was 110/60 mm. Hg. Roentgenography showed increased heart size due to left ventricular enlargement and ... dilated, pulsatile thoracic aorta. The electrocardiogram was now normal.

His condition remained unchanged for almost tw ... years u ... til March 1965 when ... t 16 years of age, he was admitted to the hospital because of the development that day of sharp left anterior chest pain ... hile j ... mping up to the net with ... basketball. The pain had become progressively severe w ... th radiation int ... the left neck and intensification on recumbency and on deep inspiration. Examination revealed ... young boy ... eighing 145 pounds and measuring 74 inches tall in no acute distress. The apical systolic murmur and aortic diastolic blow ... ere similar t ... those previously noted; the blood pressure was 150/70 mm. Hg.

X-ray showed marked increase in the size of the aorta and left ventricle and on fluoroscopy the aortic pulsations were now diminished compared with earlier studies. On venous angiogram aortic dissection could not be visualized. Serial electrocardiograms were consistent with acute pericarditis.

Because he continued symptomatic with progressive evidence of aortic dissection and increasing aortic insufficiency surgery was performed on the fourth day. Here there was found an intimal tear extending approximately one half of the circumference of the aorta 1 cm above the level of the coronary ostia. The aortic annulus was markedly dilated but there was no retrovalvular dissection by hematoma.

The area of dissection was replaced by 4 cm. long Teflon graft and the aortic valve by a Starr-Edwards prosthesis. Unfortunately continued oozing occurred from all operative sites, and despite repeated transfusion and use of hemostatic modalities the patient died.

At postmortem examination the heart weighed 715 grams with marked thickening of the left ventricular wall. The root of the aorta was markedly dilated measuring 11 cm. in diameter and showed additional evidence of dissection. The pulmonary arteries were normal as were the pulmonary and tricuspid valves. The mitral valve ring was markedly dilated, and its margins showed edematous thickening. In the posterior wall of the left atrium above the posterior leaflet of the mitral valve there roughened trabeculated area 0.5 cm. in diameter. Microscopic examination of the aorta revealed cystic medial necrosis. The mitral valve and the area of roughened endothelium in the left atrium showed fibromyxomatous thickening.

In this family the mother (Ru. B) and two sons (Ro. B and W. B.) were known to have Marfan's syndrome. W. B., two years older than Ro. B., had skeletal and ophthalmologic manifestations similar to his brother but no demonstrable cardiac involvement. He is now serving in the Army in Vietnam. All siblings were in foster homes and the two younger daughters could not be brought in for examination but are said to be well.

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NOTICE: Beginning January 1970, abbreviations for journal titles in references are to follow the style used in the Cumulated Index Medicus. These abbreviations may be found in the List Index of the Cumulated Index Medicus, as well as in the publication entitled *List of Journals Indexed in Index Medicus* published by the National Library of Medicine and available at nominal price from the Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. 20402.

Book reviews

THE CARDIAC SURGICAL PATIENT: PATHOPHYSIOLOGIC CONSIDERATIONS AND NURSING CARE. By Maryann Powers, R.N., B.S., and Frances Storlie, R.N., M.S. The Macmillan Company, Toronto, Ontario, 1969. 231 pages. Price $7.95.

This publication is useful for nurses responsible for the care of cardiac surgical patients. Though brief, it presents the essential problems related to the cardiac states which are concerned with surgery and the care of the patient following operations. Obviously a book of this sort must be supplemented by lectures and demonstrations not only by trained and experienced nurses, but by physicians as well. The physician and surgeon must realize that a knowledge of the content of this book is not adequate. This is well illustrated by the discussion of the electrocardiogram. Nevertheless, this is a very good and useful book for nurses preparing to care for the cardiac patient following surgery.

NEW FINDINGS IN BLOOD FLOWMETRY. Edited by Chr. Cappelen, Jr., M.D. Universitetsforlaget, Norway, 1968. 223 pages. Price $21.79.

This monograph presents the proceedings of the International Symposium on Electromagnetic Flowmetry held in Oslo. The papers are all very short but are clearly and concisely presented, there being almost 40 papers in 223 pages of text. The subjects discussed by several groups of investigators included technique, apparatus design, system calibration, evaluation of flowmeters, comparison of techniques, implanted probes in man and other animals, and clinical applications. This is a very good, though highly specialized book. Anyone who is working with blood flow, planning to study flow, or interested in the evaluation of data obtained with arterial flowmeters will find this book useful for study and to own. The participants, in their respective brief presentations, clearly indicate the many problems and applications as well as the difficulties and inaccuracies of the techniques used in measuring arterial blood flow. The discussions and bibliography are also valuable.

SELECTIVE ARTERIAL CATHETERIZATION: DIAGNOSTIC, THERAPEUTIC AND INVESTIGATIVE. By Howard Richard Bierman, M.D. Charles C Thomas, Publisher, Springfield, Ill., 1969. 602 pages. Price $15.75.

Dr. Bierman has summarized very nicely the subject of selective arterial catheterization for those who are contemplating employment of the procedure. The monograph briefly describes the history, techniques, apparatus, and anatomic considerations. This is followed by a presentation of radiographs of arterial systems for various organs and parts of the body. The author presents a fairly lengthy dissertation on the use of regional perfusion for malignant diseases. Unfortunately, as is so common, the impression is given that malignant processes are cured, when it is well known that a patient is extremely rarely if ever cured of a malignant disease by a chemotherapeutic agent, unless it be a small lesion on the surface of the body where a corrosive or extremely toxic agent that can chemically destroy the sharply localized lesion by direct application. And even then, surgery is preferable with rare exceptions. However, for those who wish to employ regional perfusion in the management of malignant neoplastic lesions, the techniques are valuable in this book. The chapter on investigative applications of arterial catheterization should be of little value to readers. Anyone who undertakes any mature investigations should know the necessary techniques. Furthermore, each research program is so individual that the techniques employed must be designed carefully and precisely to satisfy the needs of the particular study. This is a reasonably good book which should interest those embarking on a study of arterial catheterization.

SURGERY OF ACQUIRED VASCULAR DISORDERS. By Benjamin B. Jackson, M.D. Charles C Thomas, Publisher, Springfield, Ill., 1969. 460 pages. Price $22.50.

Doctor Jackson summarizes vascular surgery briefly in about 450 pages. The important problems are discussed, but the many details of importance are not included, particularly the problems related to various diseases which greatly influence the outcome of surgery, such as coronary heart disease, emphysema and chronic bronchitis, old age and many others. These are important, since much of vascular surgery is performed on old people. The discussions of surgical technique and management of aneurysms, occlusive vascular disease, and traumatic disease are good. The sections on obliterative cerebrovascular disease and coronary artery disease leave much to be desired from an over-all point of view. Unfortunately, the discussions are not critical and fail to emphasize adequately the nonsurgical care of vascular disease. The book does, however, describe techniques and can be useful to beginners in surgery and vascular surgery. The well-trained vascular surgeon or cardiovascular physician will find this book of little value. The illustrations and bibliography are well selected from the surgical standpoint.

VASCULAR DISEASES. By Prof. Ag. M. J. Tsapogas, M.D., M.Ch., & A. Hakkar, F.R.C.S., F.R.C.S.

(Ed.) F. N. Gle e F.R.C.S. F.R.C.S. (Ed.), Charles C Thomas, Publisher Great Brita n 1968 178 pages Price $8.50

It is impossible to describe all the vascular diseases 171 pages. Therefore the authors, all surgeons, merely present briefly some of their thought concerning surgical aspect of vascular diseases. They do not present the clinical manifestations and pathologic physiology sufficiently to orient the reader adequately about the diseases. The book contains merely brief discussion of their idea of surgical therapy. This book is too brief be of much use t a yone It ca be read quickly however if one interested n their approaches t the surgic l management of vascu l diseases The book certa nly not recommended, because superior ones are already available.

ATHEROSCLEROSIS PATHOLOGY, PHYSIOLOGY, AETIOLOGY, DIAGNOSIS AND CLINICAL MANAGEMENT. Edited b F. G. Schettler and G. S. Boyd, Elsevier Publishing Company Amsterdam 1969 1 029 pages.

The ever increasing importance of atherosclerosis in the mort lity r t of man justifies continuing effort to dela nd modify the course of this disease Schettler and Boyd with the assistance of other contributors, ha summarized rather extens ely the many difficulties associated w th atherosclerosis. The eleven chapters include discussions of morphology ultrastructure, histochemistry angiochemistry epidemiology hypertension diabetes, llergy nd utoimmune factors, thrombosis, plasma lipids and lipoproteins, race cl nical factors (cerebrovascular retinal), therapy (cardiac) diet hormones, and special tre me related to atherosclerosis. There are mber of excellent illustrations in color The bibliographies are ery good The uthors of the book and their contributors are Europeans who reflect the thinking from Europe bout this important t disease As would be expected, the book f ils t add any new ideas t our existing knowledge but in one book summarizes for the con enience of the readers important information. The alue of Atromid S, for example is not to be found on pages 875 to 877 Nor will the reader find any evidence that dieting w'll definitely reduce the incidence or severity of atherosclerosis. Nevertheless, in this one aluable volume there i a gre t deal of well-presented material on n extremely mportant health problem

MEDICAL AND SURGICAL CARDIOLOGY By William Cleland, F.R.C.P. F.R.C.S. John Goodwin M.D. F.R.C.P., F.A.C.C., Lawson M Donald M.A., M.D. F.R.C.P. and Donald Ross M.D. Ch.B. B. Sc. F.R.C.S. F. A. Davis Company Philadelphia, 1969 1 170 pages. Price $18.50.

This textbook on cardiology represent united joint effort of surgeons and cardiologists to about heart disease for the clinician. The authors and the four contributor h done successful job. The book includes a brief description of the important aspect of history physical examination, roentgenology cardiac catheterization, and other investigati procedures in their practice. Surgical techniques and procedures are discussed, as well as the common cardiac disease states. The embryology etiology pathophysiology natural history complications, and clinical course, symptoms, signs, prognosis, and therapy are presented wherever indicated for each disease. They are all integrated in a practical clinical manner The cardiologist and surgeon will of course find details which may differ from his own. For example, ea ly in the book on pages 26 and 27 Figures 2.1a, 2.2, 2.3 and 2.4a fail to indicate why changes in charges are produced or how the record ng electrodes are placed. If the reader nderstands the figure and the curves recorded then he is too advanced to find at least the section of the book to be useful. On the other hand, if he need t learn the mechanisms intended t be displayed, he will find it difficult to learn the electrophysiologic mechanisms involved for the illustrations presented Except for examples of this sort, this book is ell written and well organized. It provides in summary the manner n which the a thors manage their patients.

PULMONARY ARTERIOVENOUS FISTULA. By H. Eringa and H. J. Sluiter Van Gorcum & Comp. N.V. Dr H. J. Prakke & H. M. G. Prakke Assen 1969 126 pages

This book, which deals with highly specialized subject, consists of a description of clinical data on 27 patients with pulmonary arteriovenous fistula. The case presentations are very good and the roentgenograms excellent The authors include a fairly extensive bibliography with each case presentation being nicely oriented the review of the literature. Anyone interested in pulmonary arteriovenous fistula will find this to be a ery useful book.

KARDIALE ... TA D ND WIEDERBELEBUNG. By Martin Stauch Georg Thieme Verlag 1969 81 pages.

This is another small pocket-size manual in German on cardiac resuscitation. It is a useful manual for doctors, nurses nd others ho are interested in trai ing in the technique ... It is accurat and i adequately illustrated

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Editorial

The dilemma of the rejecting heart transplant

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As soon as it became obvious that the heart-lung extracorporeal machine was safe and likely to become safer, heart transplantation was inevitable and in 1961 it was confidently predicted that within a decade clinical trials would be underway. Groups throughout the world were busily engaged in studying the problems germane to heart transplantation and by the end of 1967 a great deal of valuable information was available and a great deal of thought had gone into many aspects—ethical as well as scientific. There were obvious deficiencies in this information, recently reviewed, and it was the duty of the cardiac surgeon to see that all major moves towards a clinical application were secure and this was gradually being achieved. It was particularly unfortunate, then, that the years of quiet endeavor in experimental heart transplantation were shattered by the publicity attending the first successful human heart transplant, publicity second to no other clinical procedure. It was particularly frustrating to have to dilute praise for the achievement with warnings[1] that the problems of rejection were not yet solved, as the public might be induced to believe.

Those who were familiar with the current status of heart transplantation by the end of 1967 were aware of the following points.

1. Tissue typing by the end of 1967 had only reached the stage whereby some immunologists had agreed that lymphocyte isoantigens, as demonstrated by isoantisera, were classifiable into a histocompatibility system HL-A. The fact that the genetics of tissue histocompatibility in the human could be induced to the relatively simple concept of a few allelles operating at a single locus in no way abrogated the vigor of the transplantation immune reaction or solved the problems of acute rejection. The tests devised for tissue typing were, and still are, insensitive and in many ways inadequate, and a serious prospective survey of results was not even available. Immunosuppression techniques had not changed either and so the transplantation situation had not radically altered just prior to the performance of the first human heart transplant.

2. The experimental technique devised for clinical heart transplantation involved sectioning the conducting system, and several surgeons were hesitant to accept such a technique. There were those who were disinclined to accept assurances that "Enough has been achieved, in fact, to provoke expression of the concept that only the immunological barrier lies between this day and a radical new era in the treatment of cardiac diseases."[2] Others[3] had clearly appreciated the advantages of preserving the sinoatrial node.

The immunological reaction against first set allotransplanted hearts was known to be similar in many ways to that evoked by a

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first set allotransplanted kidney It was also well known that a high percentage of even apparently well matched kidney allotransplants undergo some degree of rejection within the first three weeks after transplantation A full analysis of the natural history of the orthotopically transplanted canine heart was not available and although clinical signs of heart rejection were established there were still gaps in our knowledge especially of the terminal stages. The orthotopically transplanted heart of the dog is a difficult problem to monitor adequately and rejection as in the kidney can be fulminantly sudden so that monitoring the end stages is not easy

A vastly easier technique to manage is the canine heart heterotopically transplanted to the neck or pelvis. Both the orthotopic and heterotopic models have their advantages and disadvantages they are complementary and not mutually exclusive one can provide information which is difficult and nigh impossible to obtain in the other On the basis of many parameters of measurement—the electrocardiogram coronary flow response to steroid and isoprenaline etc.—the heterotopic heart functions in a manner similar to the orthotopically placed heart. Using epicardial leads in the apex and right atrial appendage one can monitor the heart before and after transplantation and in spite of the sheer abnormality of the heterotopic heart, the electrocardiogram returns to what it was like in the donor within a short space of time.

This model can supply information about the state of the coronary vessels at the onset of rejection and particularly when abnormal P waves occur on the electrocardiogram Sudden disappearance of the P wave in this model usually heralds the end of co-ordinated myocardial contraction and arteriography at this stage shows that there is a severe coronary spasm similar to the renal afferent vascular spasm which occurs in the rejecting allotransplanted kidney It is very doubtful if an orthotopically transplanted heart would be capable of sustaining the general circulation by the time sudden coronary spasm has occurred and consequently the phenomenon will be missed and more likely by those teams skilled in orthotopic transplantation

It should not be beyond the powers of the cardiac experimentalist to design techniques aimed at monitoring the coronary vessels during the natural history of the orthotopic allotransplanted heart. Although the human immune reaction is not nearly as fulminant as the canine, concern over the care and management of sudden severe cardiac rejection was uppermost in our minds.[4] It has been a feature of most human heart rejection crises that the whole process is over in a short period of time.

Of course, it was known from the work of several investigators that hydrocortisone could reverse a fall in the R-wave voltage but that this was only a temporary effect. Since the human frequently responds well to steroid there was some confidence that acute rejection could be reversed by the drug and the other immunosuppressive drugs and indeed this has proved to be the case in some patients alive and well. At the same time the price to be paid for warding off rejection might be pulmonary infection secondary to edema and/or pulmonary embolism so that the cause of death becomes merely academic when the control of a rejection episode requires so much drug therapy that infection supervenes. To survive a cardiac rejection crisis the patient must be able to tolerate and to utilize the enormous doses of steroid administered over a period of a few days. From the results of kidney transplantation in the human it could be predicted that a percentage of cardiac transplants would survive several months and that a percentage would survive episodes of rejection, but that, taken as a whole, the procedure was fraught with more problems than it could solve.

The dilemma comes in the management of the rejecting heart. On one hand, pulmonary embolism has been reported in several cases at a time when rejection was unexpected The cause of the embolism may be technical due to leaving a too bulky right atrium and leaving the recipient of a heart liable to clots which form on the suture lines. If this is a real threat then it should be no more a threat than clots on suture lines in general cardiac surgery More attention should be paid to the problem that embolism is a manifestation of heart rejection The right atrium becomes

matous, as do the other chambers of the heart during rejection, and dilates and so the scene is set for turbulence and clot formation. This is quite commonly found in the neck heart preparation and serves as a warning of possible complications in the orthotopic human transplanted heart and so heparin might profitably be administered when rejection signs are manifested. On the other hand there is the threat of further progress of rejection demanding higher and higher doses of drugs and the possibility of fulminant infection. In the meantime one will be asking the question whether it is better to cut one's losses, remove the heart, and transplant another one. If one decides on the latter one has to realize that full dosage of drugs will be required for at least ten days.

There is surprisingly little information about the second-set reaction[7] in heart transplants. It is in this situation that as many technical problems as possible affecting heart function in the early stage after perfusion must be avoided or at least recognized as such. Cooling of the heart can engender various abnormal electrocardiogram appearances and so cooling should be avoided in heart transplantation and of course, this severely limits the whole clinical application. Although cooling does produce certain abnormalities in the electrocardiogram the heart rapidly becomes pink after perfusion, but a co-ordinated beat may take some time to appear. Very different is the second-set heart which never really becomes pink and the myocardium remains somewhat cyanosed and muscular inco-ordination is more prolonged than usual after perfusion is started. Even when at about 15 minutes, a co-ordinated beat does occur the myocardium remains cyanosed and the heart rate is slow about 80 beats per minute. At 30 minutes, a crisis of systolic contraction occurs and the heart is arrested with an empty right side. Massage can start feeble muscular twitchings and it is quite remarkable that contractions can occur for some hours in spite of the fact that an arteriogram of the coronary vessels reveals intense spasm. Removed 12 to 24 hours later these hearts show signs of severe functional upset. There are numerous cells in the interstitium and they are mainly neutrophils which is an indication of a severe hemodynamic upset. There is widespread edema and hemorrhage. There is no sign of fibrinoid deposition in the capillaries despite the fact that it is reasonable to assume that the second-set antigen antibody reaction should be taking place on the endothelial surface. The fact that the coronary vessels undergo intense spasm is perhaps due to this reaction. The result of the intense spasm is widespread early signs of myocardial damage involving marked glycogen deposition in the myocardial fibers particularly those in the subendocardium. There is certainly a great difference between a first-set heart and a second-set heart at 24 hours, but since the microscopic features reveal nothing more specific than glycogen deposition one should place more reliance on the functional behavior of the heart in the early stages after transplantation and a coronary angiogram on the operating table may provide a clue as to the nature of the abnormal function. Ruling out any technical mishap, the period of warm ischemia may account for the abnormal function. Whatever causes the death of a patient may induce sorrow in the surgeon but he need suffer no shame if rejection or the effects of treating rejection are responsible. Therefore, clear responsible statements about rejection are essential.

The clinical point in all this is that individual specificity of tissues is no longer a transplantation law for the larger mammals including man. Specific individualism is a matter for rodents and is quite misleading. So if a second heart transplant is contemplated one has to consider that cross sensitization is a very real phenomenon and rapid rejection can be expected in a proportion of cases (45 per cent for skin grafts in humans)[8] and success in a few. When the situation justifies transplanting a second heart the biological test is supreme in revealing whether or not cross sensitization is a reality.

Since Fernbach and associates (1969) tissue typed their patients, their data should provide the relevant information concerning an overlap of HL A antigens in the first and second heart transplant performed in their clinic which would explain the already predicted rapid rejection of the second heart transplant. If there is a demonstrable HL A antigen overlap it

would go some way in demonstrating the anatomical basis of cross-sensitization If this evidence is found lacking cross-sensitization may be explained by a broad spectrum of polyspecific antibodies evoked by the first heart allotransplant

In terms of a rising incidence of myocardial damage severe enough to require a heart transplant most clinical programs will barely deal with 0 5 per cent of the cases since donors, hospital facilities and finances are not yet geared in this direction The logistics are considerable but steady progress and organization may yet allow heart transplantation a permanent place in cardiac surgery *There is no question that* a new heart is the answer to a severely damaged heart and indeed this conclusion is the starting point of all organ transplantation In this sense it is sound medical treatment. There is no doubt that when a heart transplant is successful the patient is better off than with any other kind of treatment this is the continuing stimulus to solve the problems Nothing particularly new was proved by the incursion into human heart transplantation Indeed the prematurity was not only at a scientific level but at an ethical level as well as it so turned out It is particularly unfortunate that some cardiac surgeons found the[illegible] selves working under conditions of [illegible] and even criminal liability Nonethele[illegible] experimental work must continue and [illegible] to be hoped it will continue in the [illegible] relentless way it has in the past.

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Clinical communications

Prolongation of isovolumic contraction time in left bundle branch block

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This study was undertaken to understand more clearly certain auscultatory abnormalities of complete left bundle branch block (LBBB) namely the frequent findings of a soft first heart sound and reversed spl tting of the second heart sound The duration of the phases of left ventricular systole were compa ed in patients w th chronic complete left bundle branch block and normal subjects. Two add tional patients w th intermittent left bundle branch block served as their own controls and were analyzed separately Th interval from th onset of the QRS complex of th electrocardiogram to the onset of isovolu contraction was examined to determin whether the interval was prolonged as has been suggested by phonocardiography o normal as has been described at cardiac catheterization in patients with LBBB

We have found that although this interval (Q-M) was significantly prolonged it was the marked prolongation of isovolumic contraction t me that was ma nly respons ble for delayed aortic val e closure.

Method and materials

Studies were performed n 25 patients with electrocardiographic evidence for complete left bundle branch block according to the criteria of W lson and associates[4] and in 29 normal sul jects. Two add tional patients h d interm ttent complete left bundle branch block

The average age of the normal subjects was 53.8 (50 to 68 years) whereas the patients averaged 66 1 (51 to 82 years) A erage heart r te was 66 7 beats per minute in normal sul jects and 66 2 per m nute in patients w tl LBBB Normal ty was determ ned l history physical examination blood pressure a 12 lead electroc rdiogram and chest roentgenograms. In the normal group there were 21 men and 8 women There were 13 men ar d 12 women w th LBBB Only 3 of the 25 patients had cle clin cal evidence of m ld heart failure although 18 were taking digitalis.

The d tio of the phases of left ventricula systole was measured from simul taneous record ngs of the electrocard ogram the phonocardiogram and the indi rect carotid arterial pulse employing a ultichannel Sanborn photographic re corder and microphone Respiration was recorded as well according to a previously described method Recording were obta ned at a paper speed of 75 mm per

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Table I Comparison of systolic time intervals in normal subjects and patients with left bundle branch block

Parameter	Normal (29)		LBBB (25)		P value
	Mean	S.E.	Mean	S.E.	
Q-M	062	002	073	003	< [illegible]
ICT	043	005	089	004	< [illegible]
LVET	297	006	268	003	< [illegible]
PEP	106	005	162	004	< [illegible]
R R	900	019	906	035	> 9

Abbreviations LBBB Left bundle branch block S.E., standard error of the values; Q-M_1 interval between onset of QRS complex and onset of first heart sound ICT calculated isovolumic contraction time; LVET left ventricular ejection time PEP pre-ejection period; R-R, R-R interval
All intervals expressed in seconds. Numbers of subjects noted within parentheses.

second The onset of the mitral closure sound (M_1) and the aortic closure sound (A_2) was measured only if the initial high frequency vibrations of these sounds were clearly defined A fourth heart sound (S_4) was differentiated from M_1 by its timing it invariably preceded the QRS of the electrocardiogram The Q-M interval was measured from recordings obtained over the mitral and tricuspid areas using low cut-off frequencies of 50 and 100 cps. The Q A interval was recorded with a microphone placed over the pulmonic and aortic areas using low cut-off frequencies of 100 and 200 cps

Systolic time intervals were measured and calculated according to the system proposed by Weissler and associates.[4] The Q-M_1 interval the interval from beginning of depolarization to the first heart sound was derived by subtracting the M_1 A_2 interval from the Q-A_2 interval The left ventricular ejection time (LVET) was measured from the beginning upstroke to the trough of the incisura of the carotid arterial pulse tracing The isovolumic contraction time (ICT) was derived by subtracting LVET from the M_1 A interval The pre ejection period (PEP) was derived by subtracting LVET from the Q-A_2 interval Statistical analyses were performed utilizing the Student t test of significance. All intervals were calculated from the mean of measurements made on 10 consecutive beats occurring during mid to late expiration each read to the nearest 5 msec. Heart rate was calculated from the relationship 60 divided by the average R R interval

Results

The results of this analysis are shown in Table I In patients with complete left bundle branch block the Q-M_1 interval was significantly longer ($p < .001$) isovolumic contraction time was significantly longer ($p < 001$) pre-ejection period was also significantly longer ($p < 001$) and left ventricular ejection time was significantly shorter ($p < 001$) It has been shown that systolic time intervals should be corrected for heart rate when groups of subjects are compared.[4] Correction for cycle length was not performed in this study however because the heart rates (mean and distribution of values) in our normal group and patients with LBBB were not different ($p > 9$) as shown in Table I

These results are shown graphically in Fig 1 Aortic closure was delayed in the group of patients with LBBB because both components of the pre-ejection period were prolonged That is both the Q-M_1 interval and isovolumic contraction time were prolonged Total systole was prolonged even though LVET itself was significantly shortened It is apparent that it was a lengthened ICT which was mainly responsible for the delay in aortic valve closure and reversed splitting of the second heart sound (S_2 We found reversed splitting in 84 per cent of patients a single second heart sound in 1? per cent and a single second heart sound

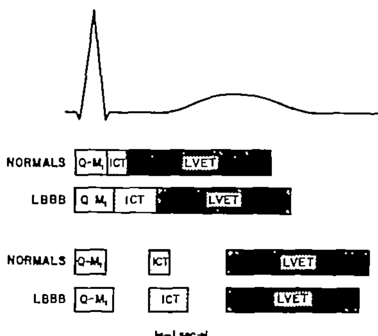


Fig. 1. Graphic representation of systolic time intervals in normal subjects and in patients with left bundle branch block. *Q-M1* Interval between onset of QRS complex and first heart sound. *ICT* calculated isovolumic contraction time. *LVET* left ventricular ejection time. *Q-M1* plus *ICT* equals pre-ejection period. *Q-M1* plus *ICT* plus LVET equals total electromechanical systole.

in expiration with audible inspiratory splitting in 4 per cent.

Reversed splitting of S_2 was not found in any of the 29 normal subjects. In 34.5 per cent of our group of normal older adults splitting of S_2 was inaudible in expiration (split $\leq$ 0.02 sec.) but audible during inspiration (split $\geq$ 0.03 sec.) In 58.6 per cent of the normal group S_2 was single on auscultation in both expiration and inspiration (split $\leq$ 0.02 sec.) Audible expiratory splitting of S_2 (split $\geq$ 0.03 sec.) was found in only 2 normal subjects, ages 52 and 53 (6.9 per cent) in the recumbent posture.

Audible expiratory splitting of S_2 disappeared on assumption of the sitting posture in both normal subjects. In patients with LBBB reversed splitting of S_2 was unchanged or exaggerated while sitting (because of earlier pulmonic valve closure in expiration). In one patient a single S_2 was recorded while supine and reversed splitting was observed while sitting.

Because all of our patients with LBBB probably had underlying heart disease, the contribution of the abnormal depolarization itself was evaluated in two patients with intermittent complete left bundle branch block (ILBBB) who served as their own controls. Intermittent LBBB occurred spontaneously in both subjects who were well and compensated. This occurred in the absence of any measurable change in heart rate in either subject.

A continuous recording which demonstrates intermittent LBBB in Patient C. H. is shown in Fig. 2. All QRS complexes were of sinus origin. The Q-M_1 interval (designated Q-S_1) did not lengthen during LBBB. The LVET was unchanged. Total systole was prolonged and reversed splitting occurred during abnormal conduction. This was owing entirely to a significant prolongation of the ICT (designated S_1-E). The first heart sound was much softer during LBBB.

A soft first heart sound was suspected on auscultation in almost all of our patients with chronic LBBB. The change in intensity of the first heart sound was documented in Patient M. R. who also had intermittent LBBB (Fig. 3). Again it could be demonstrated that paradoxical splitting of S_2 was owing entirely to prolongation of the ICT

ECG

Expiration

Inspiration

Expiration

Aortic area

Q S_1 E

Tricuspid area

S_1 P_2 A_2

Indirect carotid pulse

Recording continued

Expiration (cont.)

Q S_1 E

S_2

S_1

Fig. Continuous recording ... patient (C. H.) with intermittent left bundle branch block. Q, onset of QRS complex; S_1, onset of first heart sound (M_1); E, onset of left ventricular ejection; P_2, pulmonic ... sound; A_2, aortic ... closure sound.

Q-S_1 equal interval between onset of QRS complex and first heart sound; S_1-E eq... ... time. Note Q-S_1 was unchanged but isovolumic contraction time ... markedly prolonged ... and was responsible for reversed splitting of the second heart sound.

Fig. 3 Example of intermittent left bundle br[illegible] block. [illegible]tient M. R. 60-[illegible]-old. The change [illegible] tensity of the first heart sound em[illegible]phasized [illegible] enlargement shows [illegible] the lower panel. Left bundle branch block labeled [illegible] and the normal situation b.

Hence both patients with chronic and intermittent LBBB would seem to have in common the findings (1) prolongation of total left ventricular systole secondary to prolongation of ICT and (2) diminution in the intensity of the first heart sound Prolongation of Q M_1 or shortening of LVET was not seen in either subject with intermittent LBBB

A prominent S was recorded in 60 per cent of patients with chronic LBBB (15 of 25) but in neither of the two patients with intermittent LBBB

Discussion

There are a few case reports of hemodynamic studies during intermittent left bundle branch block.[3,7] The interval between the onset of the QRS complex and the onset of left ventricular contraction was not prolonged when left ventricular pressure was measured In 5 cases of fixed LBBB catheterized by Braunwald and Morrow[8] the onset of contraction in the left ventricle was not delayed or occurred within 0 01 sec of the onset in the right ventricle Isovolumic contraction times were not reported by the authors.

Although our average patient and that of Oravetz and co-workers demonstrated a significantly prolonged Q-M interval not all of our patients did In fact the Q-M_1 interval was less than 0 071 sec (mean plus 1 S D in normals) in 6 of 25 patients. One explanation for the discrepancy between cardiac catheterization studies and phonocardiographic studies is that patients with normal Q-M_1 intervals suffer not from block in the main bundle but rather from arborization block in smaller branches of the conduction system or within the left ventricular myocardium[9,10] Hence differences between studies could be explained by case selection

An alternative explanation resides in the significance of the markedly prolonged isovolumic contraction time. If pressure is developed slowly in the left ventricle and if left atrial pressure is somewhat elevated the onset of left ventricular contraction could precede mitral closure by 0 01 sec. the average difference in Q-M_1 intervals found in our two groups of subjects Weissler and associates[4] have reported a comparable prolongation of Q-M_1 as a result of heart failure alone in the absence of LBBB Of interest, ICT was also significantly prolonged in heart failure[4] but not to the degree found in our patients with LBBB. Hence, part of the prolongation in pre-ejection time in LBBB could be explained by heart failure.

A soft first heart sound was suspected on auscultation in almost all of our patients. Loud fourth heart sounds or atrial gallops are common in patients with LBBB[1,4] and may be confused with the first heart sound on auscultation The 64 per cent incidence of fourth heart sounds in LBBB reported by Oravetz and associates[1] compares closely with our own findings (60 per cent). Quantitation of a decrease in intensity of the first heart sound is difficult in patients with chronic LBBB but can be demonstrated clearly in the patient with intermittent left bundle branch block.

There is reason to believe that the loudness of the first heart sound is primarily determined by the rate of deacceleration of ventricular filling following atrial systole and the rate of development of pressure at the onset of left ventricular isovolumic contraction[10,11] If the latter is reduced in left bundle branch block as is suggested by a prolonged ICT the first heart sound would be diminished Widening of the first sound with separation of the components could also contribute to the reduced intensity[11]

In the case of intermittent left bundle branch block studied by Bourassa and coworkers[3] there was a fall in systolic pressure in the left ventricle a decrease in cardiac index prolonged isovolumic contraction and relaxation and a shortened diastole during LBBB

There is reason therefore to speculate that LBBB itself over and above the underlying heart disease, prolongs isovolumic contraction The associated asynchronous contraction may result in decreased force and velocity of left ventricular contraction LBBB mimics heart failure in that the pre-ejection phase is prolonged, but, in part, for different reasons. In both, left ventricular ejection time is shortered which probably reflects a decreased stroke volume

Summary

Phonocardiograms were recorded in 25 patients with chronic complete left bundle branch block (LBBB) and were compared

with findings in 29 normal subjects of comparable age. Two additional patients with intermittent left bundle branch block served as their own controls.

In left bundle branch block

1. The common auscultatory impression of diminished intensity of the first heart sound was demonstrated in patients with intermittent LBBB
2. The average Q-M interval was significantly prolonged in chronic LBBB but was unchanged in intermittent LBBB
3. The average Q-A_2 interval was significantly prolonged, resulting in paradoxical splitting of the second heart sound in 84 per cent of patients.
4. Isovolumic contraction time of the left ventricle was significantly prolonged and was mainly responsible for delayed aortic valve closure.
5. Left ventricular ejection time was significantly shortened which may reflect a decreased stroke volume.

Prolonged isovolumic contraction of the left ventricle is the most important alteration in the time relationships of ventricular contraction in patients with LBBB It may be associated with asynchronous contraction which results in diminished force and velocity of contraction of an already compromised left ventricle in many patients

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Acute hemodynamic effects of ethanol on normal human volunteers

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A relationship between chronic ethanol ingestion and heart disease has been suspected for almost a century[1] Numerous epidemiologic biochemical hemodynamic and histochemical studies have thus far failed to implicate alcohol as a direct cause of heart disease Moreover studies of the acute hemodynamic effects of alcohol have produced variable and conflicting results, depending in part on the experimental subject used

In 1930 Grollman reported that small amounts of alcohol produced a transient rise in heart rate blood pressure and cardiac output in nondrinkers, while larger amounts were required to produce these changes in alcoholics In a study of chronic alcoholics Wendt and associates found that those with clinical evidence of heart disease had a lower cardiac output and stroke volume at rest and after exercise than those without obvious heart disease Regan and co-workers gave 8 chronic alcoholics with no evidence of heart disease 110 Cm. of alcohol over a hour period Stroke volume decreased maximally at about 2 hours. Left ventricular end-diastolic pressure rose 5 mm Hg at one hour and remained elevated for the 4 hour duration of the experiment The blood level was less than 150 mg /100 ml. at the time of the maximal hemodynamic changes Simultaneous biochemical determinations disclosed a release of serum glutamic oxaloacetic transaminase potassium and phosphate into the coronary sinus blood The metabolic changes were reproduced by sucrose infusions which duplicated the osmolality changes caused by ethanol The Wendt group on the other hand was unable to detect significant hemodynamic changes in chronic alcoholics 30 minutes after the ingestion of 6 oz. of chilled vodka

Contradictory observations have been especially common in animal studies Following the intravenous infusion of ethanol over a 20 minute period in anesthetized dogs Ganz[4] found a 5 per cent decrease in the cardiac output and the stroke volume with no significant change

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in the heart rate or arterial pressure. There was a slight increase in the coronary blood flow. In dogs observed for 5 hours after a 2 hour infusion of 15 per cent ethanol at a rate of 0.1 mg. per kilogram per minute, Regan and associates[7] noted a significant fall in the cardiac output and in the contractility of the left ventricle, while the end-diastolic pressure was elevated. In still another study on dogs small to moderate doses of ethanol given intravenously caused a rise in the cardiac output, stroke volume and arterial pressure with no change in the heart rate and a decrease in the coronary blood flow.[8] Large doses (5 Gm. per kilogram) produced hypotension, a rapid rise in atrial pressure, and death due to cardiac failure. The chronic administration of ethyl alcohol to rats for 4 months resulted in a consistent decrease in isometric systolic tension, blood pressure and heart rate. In another study an attempt was made to separate the primary myocardial effects from those secondary to the peripheral effects of alcohol. In heart-lung preparations the venous return, heart rate, and afterload were kept constant while ethanol was infused. Fifteen minutes later no significant change was found in the rate of rise of ventricular pressure (dP/dT) or the left ventricular end-diastolic pressure despite blood alcohol levels over 600 mg./100 ml.

The conflicting nature of these reports seems to be related to the length of the period of observation and to the choice of experimental subjects. Those studies which failed to show significant changes after the ingestion of alcohol involved less than one hour of observation. Those which have shown changes after alcohol were done on chronic alcoholics or on animals. For these reasons it was determined to attempt to assess the acute hemodynamic effects of a moderately large oral dose of ethanol in normal human subjects observed for at least 90 minutes after alcohol ingestion.

Methods

Seventeen paid volunteers, who ranged in age from 18 to 33 years, entered the laboratory having abstained from eating and smoking for at least 4 hours and from alcohol for at least 12 hours. All subjects had a control blood alcohol level of zero. Ten were test subjects and 7 served as controls. A history of alcohol consumption was obtained on all subjects to exclude those with a history of more than moderate ethanol intake considered to be 3 oz. of whiskey or 2 bottles of beer per day. All measurements were made with the subjects in the supine position.

A Cournand needle was inserted into the brachial artery of one arm and a short, flexible cannula into an antecubital vein of the other arm. The heart rate was monitored by a continuous electrocardiogram and the arterial pressure was sensed by a Statham P23Db strain gauge on a Gilson multichannel recorder. The pressure signal was led into a Sanborn Model 150 recorder for greater amplification and inscription at a paper speed of 100 mm. per second in order to facilitate measurement of rate of rise of arterial pressure (dP/dT). The cardiac output was estimated by the dye dilution method using indocyanine green dye.

After control measurements were made the subjects bicycled on an ergometer in the supine position for 5 minutes at 100 watts. The cardiac output and arterial pressure were recorded during the fifth minute of exercise and 5 minutes after exercise. Following this, 10 subjects (age range 18 to 33 years, mean 25.8) were given 6 oz. of chilled 90 proof bourbon whiskey (81 Gm.) to drink in less than 10 minutes. The 7 control subjects (age range, 20 to 29 years, mean 24.4) merely lay on the bed for 10 minutes. At 15, 30, 60, and 90 minutes after the ingestion of the whiskey, blood was drawn for estimation of the alcohol level and the cardiac output, heart rate, arterial pressure, and dP/dT were measured. The subjects then exercised on the ergometer for 5 minutes at 100 watts. Exercise and 5 minute recovery records were taken as before.

Results

Blood alcohol levels. Peak blood alcohol levels were reached within 30 minutes in the majority of subjects and within 60 minutes in all except one. Peak levels ranged from 85 mg./100 ml. to 136 mg./100 ml. The results are summarized in Fig. 1.

Hemodynamic findings. The two groups

were quite similar in the control period. The heart rate was 67 beats per minute in the control group compared to 69 beats per minute in the alcohol group. The cardiac index was [illegible]7 L. per minute per square meter in the control group and 2.6 L. per minute per square meter in the alcohol group. The stroke index was [illegible] ml. per square meter in the control group and 38 ml. per square meter in the alcohol group. The brachial artery dP/dT was 511 mm. Hg per second in the control group and 479 mm. Hg per second in the alcohol group.

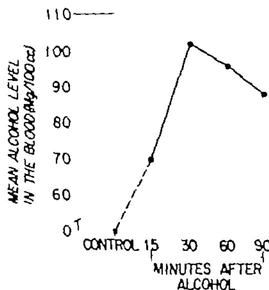


Fig. 1. Mean blood ethanol levels in 10 subjects following the ingestion of 81 Gm. of ethanol.

EFFECTS OF EXERCISE. During the first exercise period the cardiac and stroke indices rose in both groups. The heart rate response was the same in both groups. The response to the second bout of exercise 90 minutes after alcohol was similar in both groups. The response to exercise of the alcohol group before and after alcohol was identical. The hemodynamic effects of exercise are illustrated in Fig. 2.

EFFECTS OF ALCOHOL. Figs. 3 and 4 show the effect of alcohol on the heart rate and the cardiac index. Both increased following the ingestion of alcohol. Thirty minutes after alcohol the changes in cardiac index in the alcohol group were significantly greater than in the control group at the 5 per cent (one-tailed) level of significance (Student t distribution was used in measuring significance. In some cases because of

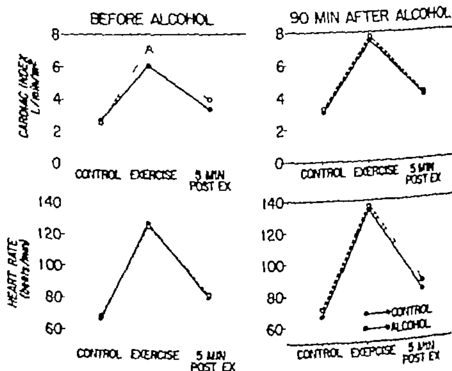


Fig. 2. Effect of supine exercise on a bicycle ergometer at 100 watts on heart rate and cardiac index before and 90 min. after alcohol.

unequal sample sizes and unequal sample variances, Cochran and Cox's[11] approximate test utilizing a weighted mean of tabular t values for the two samples was used.) In 9 of the 10 subjects in the alcohol group the cardiac index 30 minutes after alcohol was higher than the control value and in 7 of these the increase was greater than 10 per cent. In the control group 3 out of 7 had an increase in the cardiac index of greater than 10 per cent, while the other 4 had a slight decrease. The increase in heart rate was significantly greater in the alcohol group than in the control group at the 10 per cent level.

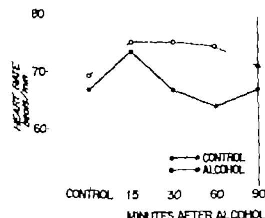


Fig. 3. Heart rate response following alcohol in the alcohol group compared with corresponding measurements made in the control group.

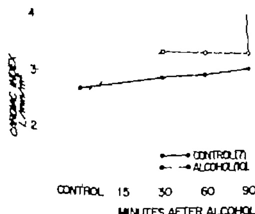


Fig. 4. Changes in cardiac index following alcohol in the alcohol group compared with corresponding measurements made in the control group.

Seven out of 10 of the alcohol group had an increase in heart rate of greater than 10 per cent whereas none in the control group did.

Differences in stroke index and arterial dP/dT changes were not significant at the 5 per cent level. Arterial blood pressure tested at the 10 per cent (two-tailed) level was also not significant (Table I). It is realized, however, that minor differences in dP/dT may not have been appreciated due to the rather poor frequency response of the recorder. There was a tendency for the cardiac index and the stroke index to increase gradually over the 90 minute period in the control group but the magnitude of this rise was not significant compared to the changes observed in the alcohol group.

Since the blood flow increased without a change in arterial pressure after alcohol the calculated peripheral resistance decreased after alcohol (Table I).

Discussion

Although there is an apparent association between chronic alcohol consumption and heart disease, there is no consistent evidence that alcohol causes acute alterations in circulatory dynamics. Of patients with heart disease of obscure etiology, 60 to 85 per cent have a history of moderate to heavy alcohol intake.[12,13] Recently electron microscopic and histochemical studies have demonstrated findings which may be specific for alcoholic cardiomyopathy.[14,15]

Previous investigations in man which have shown a *decrease* in the cardiac output after alcohol have been performed on chronic alcoholics. The present study on normal subjects showed an *increase* in cardiac output maximal 30 minutes after alcohol, accounted for mainly by an increase in heart rate since the stroke volume showed little change. This variability of response could be due to the presence of subclinical heart disease in chronic alcoholics. Alcoholic cardiomyopathy may be merely one phase in a spectrum of heart disease which has a high output thiamine responsive state (beriberi) at one end and low output nonthiamine responsive states at the other. If this is a valid assumption it may partly account for the extremely

Table I

Parameters	Group	Before alcohol: Rest	Before alcohol: Exercise	Before alcohol: 5 min. after exercise	After alcohol: Minutes after alcohol 15	30	60	90	Exercise	5 min. after exercise
Stroke index (ml./M.²)	Alcohol	38	56	49	41	45	44	43	[illegible]	[illegible]
	Control	42	43	42	39	45	43	43	[illegible]	[illegible]
Arterial ΔP ΔT (mm. Hg/sec.)	Alcohol (7 subjects only)	479	1113	549	533	471	567	513	[illegible]	[illegible]
	Control	511	1218	584	545	509	569	542	[illegible]	[illegible]
Systolic pressure (mm. Hg)	Alcohol	102	144	99	100	94	100	97	[illegible]	[illegible]
	Control	96	153	99	103	100	104	110	[illegible]	[illegible]
Diastolic pressure (mm. Hg)	Alcohol	63	79	60	63	62	62	60	[illegible]	[illegible]
	Control	67	94	64	69	68	71	78	[illegible]	[illegible]
Mean arterial pressure $\left[P\,dias. + \left(\frac{P\,sys. - P\,dias.}{3}\right)\right]$ (mm. Hg)	Alcohol	73	101	73	75	73	73	[illegible]	[illegible]	[illegible]
	Control	71	104	69	[illegible]	72	73	90	111	[illegible]
Peripheral resistance (dynes/sec./cm.⁻⁵)	Alcohol	1104	540	893	913	920	900	[illegible]	[illegible]	[illegible]
	Control	1063	695	815	1054	994	1018	1004	[illegible]	[illegible]
Heart rate (beats/min.)	Alcohol	68	125	83	73	73	74	71	[illegible]	[illegible]
	Control	67	127	81	73	67	64	67	[illegible]	[illegible]
Cardiac index (L./min./M.²)	Alcohol	2.87	7.21	3.96	2.99	3.36	[illegible]	3.25	[illegible]	[illegible]
	Control	2.69	6.04	3.41	2.81	2.90	2.94	3.03	[illegible]	[illegible]

variable results in investigations of the hemodynamic effects of alcohol cited earlier Thus following stress with angiotension the stroke index increased and the left ventricular end-diastolic pressure rose in normal subjects, while in chronic alcoholics without overt heart disease a rise in end-diastolic pressure was not followed by an increase in stroke index.[4] The alcoholics had impaired contractility of the left ventricle attested by a lower maximal rate of pressure rise than the normal subjects.

The response to alcohol may indeed be altered by many years of alcoholic consumption obviated in our study by the use of normal subjects. Finally the subjects in the present study are youthful The possibility that the response to alcohol may change with age has not been investigated

Both in animals and in man the hemodynamic changes are maximal about 2 hours after the administration of alcohol. It has been postulated that acetaldehyde, a metabolic product of ethyl alcohol, rather than alcohol itself accounts for these late changes. In dogs, James and Bear [6] have shown an increase in heart rate after acetaldehyde while ethanol had no chronotropic effect The infusion of acetaldehyde in humans is followed by a rise in the heart rate and an increase in oxygen consumption [17] It is believed that these effects are mediated by catecholamines released by acetaldehyde from the myocardium [18,19]

Summary

Data on the acute hemodynamic effects of alcohol in human subjects are conflicting. In the present study there was a significant increase in the cardiac output in the 10 young normal subjects 30 minutes after the ingestion of 6 oz of 90 proof bourbon whiskey due to an increase

the heart rate without a change in stroke volume. The arterial pressure was unchanged. Left ventricular contractility (dP/dT) was unimpaired. Alcohol had no effect on the hemodynamic response to a work load of 100 watts for 5 minutes. These findings conflict with previous observations on middle-aged chronic alcoholics. The variability noted in these earlier observations may be due partly to the effect of age itself but more probably and importantly to subclinical cardiomyopathy in chronic alcoholics.

We gratefully acknowledge the statistical assistance of Mr. Douglas Gause.

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Clinical, hemodynamic, and surgical considerations of rupture of the ventricular septum after myocardial infarction

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Among the various complications of acute myocardial infarction, perforation of the ventricular septum is one of the earliest to be recognized by pathologist and clinicians. Many cases have been reported in the past, singly or in groups, and excellent reviews are available.[1-4] However, in recent years this clinical entity has been considered in a different light, for it has been shown that successful repair of such acquired defects is possible. This communication deals with a series of patients presenting postinfarctional septal perforation who underwent careful clinical and hemodynamic studies. It is our purpose to review this subject in the light of surgical consideration.

Material and methods

This report includes 10 cases of postinfarctional perforation of ventricular septum; 9 patients were treated in this hospital. Hemodynamic studies were performed in 8 patients and in 6 open-heart surgery was performed for closure of the defect. The series represents all cases in which this diagnosis was made. However, some of the patients were transferred here from other hospitals for surgical considera- tion, so that the series cannot be looke[d] upon from the standpoint of the frequen[cy] of septal perforation in acute myocard[ial] infarction. Clinical studies included phy[si]cal examination and electrocardiograph[ic], phonocardiographic (whenever feasib[le]), and roentgenographic examinations. Ca[r]diac catheterization was performed u[sing] the standard techniques but did not i[n]clude an exercise stress test because of t[he] precarious condition of most patients.

Findings

This series consists of 10 cases. The[re] were 8 men and 2 women (Table I). Th[e] ages ranged from 52 to 72 years, wi[th a] mean of 6?.5 years. Anatomic confirmatio[n] of the diagnosis was available in 9 patie[nts], 8 of whom had necropsies performed a[nd] 6 had description of findings at the ti[me] of the operation. Thrombotic occlusion o[f] a major coronary artery was found i[n]

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cases the eighth had a subtotal occlusion of the right coronary artery by a plaque All patients had myocardial infarction involving the free wall of the left ventricle in addition to the septal involvement In the 8 patients in whom a detailed description of the heart was available 2 had a small posterior myocardial infarction two had moderate-sized posterior myocardial infarcts, 4 patients had massive myocardial infarcts, one had apical infarction two had anterior wall infarcts, and one had posterior wall infarct. In 5 patients an aneurysmal bulge of the free wall of the heart was noted Perforation of the septum was in all cases located within larger transseptal infarction as a rule an extension of the free wall infarct It was located in the apical portion of the septum in 3 patients, in the midportion in 2 in the posterobasal part in 3 and in the anterobasal in 1 case

Review of the clinical data revealed that all patients had a fairly typical onset of acute myocardial infarction The appearance of the murmur—signifying perforation of the septum—occurred 1 to 6 days after the initial attack the average time of rupture being 2 6 days after the infarct. This event was associated in 8 patients with a sudden worsening of condition ranging from the appearance of signs of cardiac failure to severe shock. The murmur was recorded as harsh and loud in all cases except one in which a high frequency musical quality of the murmur was noted. The intensity of the murmur at the point it was loudest was estimated as Grade 3 to 5 using the six-scale grading method The point of maximum intensity of the murmur was located at the lower left sternal border (third to fifth intercostal spaces) in 4 patients and in the apical area in 3 patients. In 3 patients the murmur was thought to be of equal intensity at the apex and the left sternal border In 6 patients radiation of the murmur to the axilla was commented upon The presence of a systolic thrill was recorded in 3 patients however this is probably an underestimation due to our opinion that a thrill is not a clinically important sign and contributes practically no information un available by auscultation Most patients showed some evidence of cardiac failure both left and right ventricular failure appeared to be present in most. Evidence of elevated venous pressure was, as a rule present and evident by examination of the jugular venous pulse at the same time pulmonary venous congestion was evident on chest roentgenograms and by the frequent presence of pulmonary râles. Electrocardiogram showed the expected changes of myocardial infarction in addition in 5 of the 10 patients persistent RS-T segment elevation was present which correlated well with the anatomic evidence of cardiac aneurysm Surgical intervention was done in 6 patients, 11 14 16 18 28 and 43 days after the onset of the myocardial infarction and 8 11 1 16 27 and 39 days after septal perforation The 4 unoperated patients survived infarction 14 days, 2 years, and 3 years respectively one patient is alive 18 months after the infarction

A review of surgical results indicates that in one patient (Case 4) the ventricular septal defect could not be closed because of the extensive necrosis of the ventricular septum surrounding the septal defect In another (Case 10) refractory ventricular fibrillation occurred as the skin was being sutured following closure of the defect. Three patients died in the postoperative period from complications. One of these (Case 5) showed only slight improvement death occurred on the twelfth postoperative day from an arrhythmia and cardiac arrest. Autopsy showed a persistent small defect. The 2 other patients (Cases 6 and 8) showed prompt significant clinical improvement and evidence of complete closure of the septal defect, as there was no cardiac murmur present postoperatively

Hemodynamic data are available in 8 patients, one of whom had 2 serial studies performed (Table II) In all patients left ventricular pressures were higher than right ventricular pressures, although in 5 patients right ventricular pressures approached systemic levels. The blood was shunted from left to right in all cases. The flow ration within the circulations ranged from 1 9 1 to 4.3 1 In all patients left atrial pressures were abnormally elevated right atrial pressures were abnormally high in all but one patient. This patient's (Case 2) study was performed 1½ years after the infarction—the only one after

Table I Summary of clinical and pathological findings in 10 patients with postinfarction perforation of the ventricular septum

Case No.	Age sex	Date of infarct	Clinical status	Date murmur appeared	Change in condition	Description of murmur	ECG
1	56 M	2/10/59	Typical acute MI good condition	2/16	LV and RV failure	Grade 4 widely heard, max. LSB	IMI, present S-T elev.
2	67 M	6/12/60	Typical acute MI satis. condition	6/15	Shock and RV failure responded to treatment	Grade 4 loudest at apex thrill	IMI, present S-T elev.
3	69 F	1/9/64	Series of attacks of chest pain	1/10	No signs of failure	Grade 4, loudest at apex	IMI
4	53 M	9/28/64	Severe initial attack of MI doing well	9/30	Hypotension, borderline shock	Grade 4 loudest at lower LSB	IMI
5	62 M	10/16/64	Typical acute MI	10/18	Fall in BP tachycardia confusion, RV failure	Grade 3, equally well heard at LSB and apex	AMI, present S-T elev.
6	52 M	4/25/66	Typical acute MI	4/28	Hypotension, oliguria requiring pressor amines and isoproterenol	Grade 3, medially to apex thrill	ASMI
7	72 M	7/23/66	Recurrent attacks of chest pain over 3 days more severe pains on 7/23	7/25	More pain signs of shock appeared, temp. rose	Grade 5 at apex and lower LSB	IMI
8	69 M	9/28/66	Typical acute MI	10/3	Weakness no signs of shock or heart failure 4 days later intractable arrhythmia	Grade 4 at lower LSB thrill	IMI, present S-T elev.

...te of ...thac ...ok.	*Operation*	*Findings at operation*	*Follow-up*	*Autopsy finding*
1/20	3/27 closure by Teflon patch	2 by 3 cm. defect t pical portion of septum	8 months postoperatively doing ell	—
1/29 1962	—	—	Between ttack and study had another MI recovered, remained in moderately satis condition operation scheduled for early M y 1962 died suddenly prior t that date	Heart 540 Gm Complete occlusion of ADB nd RCA. Apex of LV bulging as large aneurysm Large fibrotic area of sept m with 3 openings largest 0 7 cm in diam (Fig 1)
—	—	—	Recovered from MI remained compensated under therapy developed AF followed by heart failure died in Aug 1967	Heart 600 Gm Several areas of narrowing of CA, no complete occlusion Area of fibrous in post all of LV and nother in post. part of septum ith smooth round defect 1 cm. diam.
1/9	10/10, tissues too necrotic for successful closure	Large perforation of posterior septum	Died t operation	Heart 575 Gm Thrombotic occlusion RCA Large posterior ll infarct extending into posterior part of septum there is defect 3 by 2½ cm surrounded by necrotic tissue
1/30	11/3 Teflon patch closure of defect near apex	Large perforation of apical and anterior sept m	Slight initial improvement then deterioration of ardia status cardiac arrest death on 11/15	Heart 580 Gm Thrombotic occl sion of LCA Anterior bulging neurysm Large infarct involving t ll and ant. 2/3 of septum with 2 by 1 5 cm perforation in nf rcted area near apex
3/1	5/6, defect closed ith I alon sponge aneurysm plicated	Large anterior wall aneurysm necrotic anterior sept m ith 2 by 1.5 cm. perforation t its anterior portion	Improvement after surgery out of shock, no heart failure Developed staph pneumonia, and thrombocytopenia died 5/28	—
—	—	—	P tient developed confusion, lethargy then seemingly irreversible CNS damage died 8/2	Heart 550 Gm Thrombotic occl RCA Post wall of LV nd post. septum showed infarction. High on post. wall of septum, 1 cm. from free all of LV oval defect, 1 cm. diam.
11	10/25, defect losed ith Dacron patch	Large necrotic area of post. septum with 1 larger nd 3 smaller perforations	Condition ery good for 2 days then dev loped massive GI hemorrhage uremia died 10/30	Heart 500 Gm. Complete occlusion RCA Moderat -sized infarct bulging as neury m t post wall of LV Infarcted post. part of septum with perforations losed by patch
—	—			

Continued on following page

Table I —Cont d

Case No	*Age, sex*	*Date of infarct*	*Clinical status*	*Date murmur appeared*	*Change in condition*	*Description of murmur*	EC
9	62 F	4/12/67	Typical acute MI	4/14	Mild signs of heart failure (left and right)	Grade 3, lower LSB (high pitched)	[illegible]
10	64 M	8/1/67	Typical, severe acute MI	8/2	Shock, cardiac arrest with resuscitation	Grade 4 at apex, softer at LSB	[illegible]

Abbreviations: LV = left ventricle; RV = right ventricle; IMI = inferior myocardial infarction; AMI & ASMI [illegible] cardial infarction RCA = right coronary artery ADB = anterior descending branch (coronary artery) LCA [illegible] AF = atrial fibrillation LSB = left sternal border; RBBB = right bundle branch block.

Table II *Hemodynamic data on 8 patients with septal perforation*

Case N	*RA (mm Hg)*	*RV (mm Hg)*	*PA (mm Hg)*	*PAW (mm Hg)*	*BA (mm Hg)*	*PF (L./min.)*	*SF (L./min.)*	*PF/SF*	*TPR (dynes sec. cm.⁻⁵)*	[illegible]
1 A. L.	18	60/18	60/24(35)	—	100/60	17 2	5 6	3 1/1	168	[illegible]
2. E S	3	78/6	74/18(42)	14	130/80	12 3	3 5	3 5 1	29	[illegible]
4 C T	15	61/6/18	65/73(32)	14	101/65	15 4	6 8	2 2/1	110	[illegible]
5 M W	15	48/14	44/20(28)	24	100/75	9 9	3 2	3 1/1	2.1	[illegible]
6 Q Y	18	60/18	60/24(35)	—	100/60	17 2	5 6	3 2/1	40	[illegible]
8 R M	15	53/19	58/20(34)	20	101/70	13 6	3 1	4 3/1	64	[illegible]
9 B H	14	66/4/16	68/23(45)	28	166/93	10 0	5 2	1 9 1	135	[illegible]
10 A. T (8/8)	16	87/5/16	37/19(76)	—	87/63	11 0	2 5	4 3/1	119	[illegible]
10. A. T (8/29)	13	53/2/13	51/17(32)	16	90/52	13 6	2 8	4 9 1	100	[illegible]

Abbreviations: RA = right atrium; RV = right ventricle; PA = pulmonary artery PAW = pulmonary artery wedge BA [illegible] artery; PF = pulmonary flow (output); SF = systemic flow; TPR = total pulmonary resistance

such a long interval The calculated systolic size of the defect (by means of the formula of Gorlin and Gorlin[4]) varied from 0 4 to 1.3 cm.[2] (0.3 to 0.8 cm [2] per square meter of body surface area)

Discussion

Pathologic anatomy Observations concerning the size and location of the septal perforations in our series show no major difference with other reported cases. Swithinbank [4] who reviewed a total of [illegible] cases reports that out of 46 cases [illegible] detailed reports 7 had the largest diam[eter] of the perforation greater than 2 cm., [illegible] 10 smaller than 1 cm Comparable [illegible] were present in our series. In Swithinbank's [illegible] review 66 per cent of the perfora[tions] were in the lower part of the septum [illegible] our series 3 patients had perforation[s] [illegible] the apical portion and ? in the [illegible] of the septum. Three patients had [illegible]

...	*Operation*	*Findings at operation*	*Follow-up*	*Autopsy findings*
3	—	—	Condition good, easily controlled with digitalis and diuretics well 1¾ years after infarction	—
1 ... ed /29 [illegible]	8/30, defect closed through left ventriculotomy	Large necrotic area of mid-septum with central perforation	Died of cardiac arrest shortly after completion of operation	Heart 630 Gm Thrombotic complete occlusion RCA 2 cm. from origin. Massive infarction of post. wall with near bulge, extending int post. part of septum, where perforation closed by patch

septal perforations, a slightly higher incidence than the 17 per cent in the collected series.

Our series confirms earlier observations that infarction of the free wall of the heart almost always accompanies septal infarction and perforation However the most interesting finding in the large incidence of cardiac aneurysms in association with septal perforation (5 of 9 cases) In reviewing illustrations, presented in other reports, it is evident that cardiac aneurysms are very common indeed,[4-11] a fact not generally recognized which appears to be of some practical significance

Pathophysiology Congenital defects of the ventricular septum are shown to fall into two categories large defects, which cause equilibration of pressure in the two ventricles, and small defects, which are consistent with preservation of a pressure gradient between the two ventricles.[illegible] Experimental production of interventricular communications merely shows a slight increase in pulmonary artery pressure without the equilibration phenomenon [illegible] Similarly hemodynamic observations in this series and collected data from other cases [illegible] do not show a single instance in which right ventricular pressure reaches systemic levels. The calculated size of the defects reveal the largest ones to be 1.3 cm.² (0.8 cm.² per square meter) It is known from observations in congenital ventricular septal defects that the critical size separating the large from the nonequilibrating septal defect is about half to one third of the aortic orifice or 1 5 cm diameter (+1 cm size) per square meter of body surface area It is probable that acquired large septal perforations cannot exist in man or the experimental animal because they are inconsistent with survival. Survival with congenital defects is made possible only by the postnatal adaptive processes. Furthermore, the location of the defect may contribute to the difference between acquired and congenital defect The critical size determining pressure equilibration is the effective size of the defect during systole Congenital defects located in the membranous septum are unlikely to change its size during ventricular contractions. Acquired defects, virtually always located in the muscular septum may become considerably smaller during systole than their size recorded at operation or autopsy a fact seemingly demonstrated by the discrepancy between observed size of defects and their calculated area in our series. Data collected by Oyamada and Queen [7] reveal that 24 per cent of 200 patients died within the first 24 hours. It is likely therefore that these early deaths eliminate all patients with larger perforations above the previously mentioned critical dividing line

The magnitude of left-to-right shunts in this series and in other reported cases varies greatly but the preponderance of



Fig. 1 Heart of patient E. S. (Case 2), showing the large area of septal fibrosis with 3 perforations and a large apical aneurysm (courtesy of the Department of Pathology, Veterans Administration Hospital, Oakland, California)

patients show large shunts in excess of 2 : 1 flow ratio. Evidence is presented that both right and left ventricular failure are as a rule present. However patients who show large shunts also most frequently have aneurysms of the left ventricle as well which are just as apt—perhaps even more apt than the perforation of the septum—to produce heart failure. The fact that patients with a large shunt *and* a ventricular aneurysm can survive 2 or more years (Case 2, Fig. 1) seems to indicate that acquired ventricular shunts are surprisingly well tolerated. This may be in part due to the distribution of the overload among both cardiac ventricles.

Clinical finding and the differential diagnosis In spite of the fact that clinical diagnosis of the postinfarctional septal perforation is made with increasing frequency (39 of 54 collected cases were diagnosed during life) this series has illustrated some misconceptions in the clinical findings which have a bearing on the differential diagnosis. The appearance of a loud murmur one to several days after the onset of acute myocardial infarction is a characteristic feature of this syndrome as is generally agreed. However the murmur is shown to be located just as frequently at the apical area as at the lower and middle sternal border. Furthermore its radiation to the axilla is common. The generally accepted view of its localization at the sternal border is undoubtedly influenced by the characteristic murmur occurring in the congenital ventricular septal defect. Yet it is clear that the anatomical location of congenital defects and postinfarctional septal perforation differ greatly. At least 90 per cent of congenital defects are located in the general region of the membranous septum; septal perforation always affects the muscular septum and can be found in a wide range of locations. The apical location of the murmur and its radiation to the axilla is undoubtedly related to the jet directed posteriorly and inferiorly and perhaps to the effect of ventricular dilatation and or the cardiac aneurysm.

The second point brought out in this series is the frequency of posterior myocardial infarction in association with septal perforation despite the common belief that the latter is typically a complication of anterior and anteroseptal myocardial infarction.[4,8] Furthermore the electrocardiogram in this series revealed a [illegible] conduction disturbance in only one case and that was known to predate the myocardial infarction (Case 9). Thus, the often quoted frequency of intraventricular conduction defects is not borne out. However a persistent elevation of the RS-T segment was present in half of our cases and permitted the identification of a coexisting cardiac aneurysm—a finding not previously noted.

The clinical course of patients after septal perforation shows considerable variation. As a rule an immediate deterioration of the patient's condition is evident and signs of cardiac failure or shock are likely to occur. However medical treatment may stabilize the patient's condition and gradual improvement is common. The possibility of long term survival is [illegible] by findings of this series. Further, Case 2 illustrated such survival even in the presence of massive myocardial [illegible] tion with an apical ventricular aneurysm.

It should be emphasized that our series, consisting largely of referred cases, is weighted toward milder cases. The

that septal perforation may be a catastrophic event leading to death immediately or within hours is evident from the literature and presumably eliminates the largest septal perforation. Such cases are not represented in this series. It is possible that some of the difference between this series and collected cases from the literature may be related to this preselection.

The differential diagnosis of septal perforation is almost entirely that of separating it from rupture of papillary muscle. Reports of the latter complication of myocardial infarction[24-27] emphasize differential points that are not borne out by our series. Findings thought to be characteristic for papillary muscle rupture, such as apical location of the murmur, its conduction to the axilla, the association with posterior myocardial infarction, the rarity of intraventricular conduction defects, and the presence of isolated left ventricular failure, are all found with equal frequency in septal perforation, making the differential diagnosis totally unreliable short of hemodynamic confirmation. The misleading beliefs regarding clinical features of these two conditions was impressive in that all of our cases in which apical murmurs were present were initially thought to be papillary muscle ruptures, a fact also illustrated by a recently reported clinicopathological conference.[11] It should be pointed out that not a single case of ruptured papillary muscle was seen in the ten year period during which the 9 cases of septal perforation were observed. This does not necessarily reflect the difference in the frequency of the two complications of myocardial infarction but rather may illustrate the fact that the great majority of patients with papillary muscle ruptures die within the first day,[7] for acute mitral insufficiency presents a more serious load upon the heart than the surviving smaller septal perforations and is comparable to the immediately fatal large septal perforations. Thus it is our opinion that the only valid clinical differential point between these two conditions is that patients who develop loud systolic murmurs after myocardial infarction and who survive the initial 2 days are much more likely to have septal perforation than papillary muscle rupture.

Surgical considerations. The feasibility of surgical repair of postinfarctional septal perforation has been clearly established as well as the long term survival of favorable cases.[18] It is generally conceded that the best chances of success are in patients who have survived several weeks prior to the operation, where fibrous tissue facilitates the repair. However, our Case 6 has demonstrated that an emergency operation in a patient in cardiogenic shock, performed 8 days after septal perforation, may have a chance of success, for in this case death was due to a delayed secondary complication, while the surgical repair of the septum succeeded in reversing shock.

The principal question is whether the presence of a large acquired interventricular left-to-right shunt constitutes per se the indication for surgical intervention. Our observations imply that such a shunt is reasonably well tolerated in patients who survive the initial period and that the presence of heart failure may be traced not only to the shunt but also to the coexisting myocardial damage and, frequently, to a ventricular aneurysm.

Thus it is suggested that surgical consideration be given to two types of patients: (1) those in the acute stage who persist in shock or severe cardiac failure unresponsive to best medical therapy, in whom a desperate surgical effort is indicated even at high risk; (2) those with healed infarction (more than 4 weeks after the perforation) who are disabled by refractory cardiac failure. In the first category, the diagnosis should be confirmed by a simple right-sided cardiac catheterization; in the second category, a more comprehensive study to include angiographic evaluation of ventricular contraction is indicated.

Summary and conclusions

The analysis presented here included 10 consecutive cases of postinfarctional septal perforation, a series weighted toward patients surviving the initial few days following this complication. The series thus includes the potential candidates for surgical treatment. The following conclusions are reached:

1. The anatomic findings as a rule include a complete thrombotic occlusion of a

major coronary artery and an infarction involving not only the septum around the perforated area but major damage to the free wall of the left ventricle Aneurysms of the ventricle are very common The perforation occurs in the muscular septum and varies from small tears to openings measuring 3 cm in the longest dimension.

2 The magnitude of the left to-right shunt through the perforation varies from 75 to 300 per cent of the systemic output, as measured by the Fick formula The systolic size of the defect ranges up to 0.8 cm^2 per square meter Pressures in the right ventricle are moderately elevated but do not reach systemic levels. In patients undergoing study during the acute stage (less than 4 weeks) biventricular failure is evident

3 Clinically septal perforation occurring within days after the attack of myocardial infarction manifests itself as a dramatic event, usually leading to cardiac failure shock or both Nevertheless, patients may respond to medical treatment and stabilize their condition through the healing stage or even make a clinical recovery

4 Contrary to widely held beliefs the frequent apical location and axillary conduction of the systolic murmur in septal perforation its common association with posterior wall infarcts and the rarity of intraventricular conduction defects may make a clinical differentiation of this condition from a postinfarctional papillary muscle rupture difficult.

5 The selection of patients for surgical repair of the perforation should be made with cognizance of the fact that the shunt may be well tolerated and the circulatory failure caused equally or even more by the myocardial damage. Two major indications are visualized the high risk early emergency operation for patients in nonresponsive shock where only occasional salvage can be expected and the elective operation of healed septal perforation in patients with persistent cardiac failure Whenever applicable septal repair should be combined with aneurysmectomy

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Heart size and ten year survival after uncomplicated myocardial infarction

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Whether enlargement of the heart following myocardial infarction can occur in the absence of hypertension heart failure or other complicating conditions still remain uncertain [2] Little information is available on the significance of heart size to prognosis in these circumstances. Accordingly our patients with atherosclerotic coronary heart disease (CHD) were selected to be free of any other condition which might affect either heart size or survival so that the problem could be properly examined

We report here that cardiac enlargement can be demonstrated by fluoroscopy and roentgenography but not by electrocardiography in one third of men with uncomplicated myocardial infarction and that this enlargement adversely influences survival over a 10 year period

Clinical material

The selection investigation and characteristics of the 105 patients have been described in detail There were approximately 26 men in each of the fourth to seventh decades inclusively All originally had unequivocal myocardial infarction and were free of hypertension defined as blood pressure above 150/90 mm Hg None had other heart defects or any other major disease None was in congestive failure As shown by the 10 year mortality experience [4] these patients could be considered a good risk group Survival was not influenced by the serum lipid lipoprotein concentrations nor by the electrocardiographic findings.[5]

Methods

Fluoroscopy A visual estimate of the heart size was made in the various projections, and the cardiothoracic ratio calculated from the orthodiagram.[7]

Teleroentgenography The transverse diameter of the heart was measured and compared to normal values established for heights and weights by Ungerleider and Gubner [8] The frontal area of the heart was calculated and compared to that predicted from height and weight [9]

Electrocardiography The electrocardiogram (FCG) consisted of the com[illegible] 12 leads recorded with the patient [illegible]

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and in the fasting state. All tracings originally had decisive changes of acute infarction, either significant Q waves or reciprocal S-T changes. The criteria for left ventricular hypertrophy and strain were those laid down by Goldberger.[9]

Results

Survival. Survival rate was determined by the actuarial or life table method.[1] The starting date for the major part of this investigation was the initial examination on entry into study in 1952 to 1954. Most previous workers used the findings at the time of acute myocardial infarction or shortly thereafter.[3] The time interval from infarction to entry into study varied from 3 to 156 months with a mean of 40 and a median of 80 months. No patient was lost to follow-up which ended Sept. 1, 1962. From time of entry into study, the cumulative 5 year survival was 64 per cent; the 10 year, 42 per cent. Age had no significant influence on 5 year survival, but by the tenth year there was, not unexpectedly, a decreased survival in the oldest decade.

Cause of death. During the study, 53 of the 105 patients died. In 27, an acute infarction was proven clinically or verified at autopsy. Coronary heart disease was presumed to be the cause of death in the 21 patients who died suddenly outside of the hospital. Only 5 deaths were noncardiac. Table I contrasts the mode of CHD death in patients with and without fluoroscopic heart enlargement. In those with enlargement, sudden death was more common than infarctional death but not significantly so.

Table I. *Mode of CHD death in relation to heart enlargement*

Group	No. of patients	No. of CHD deaths	Acute myocardial infarction	Sudden death
Without enlargement	68	22	15	7
With enlargement	37	26	12	14
Totals	105	53	27	21

*Not significantly different.

Presence of heart enlargement. The data are presented in Table II.

By fluoroscopy, the visual estimate of heart size gave results similar to those obtained by measuring the cardiothoracic ratio. By each method, 36 per cent of the patients were found to have heart enlargement.

Employing the transverse cardiac diameter of the teleroentgenogram, 35 per cent of the patients showed enlargement of 110 per cent or greater, 19 per cent enlargement of 115 per cent or greater. By the frontal area measurement, 55 per cent of the patients showed enlargement of 110 per cent or greater, 37 per cent enlargement of 115 per cent or greater.

Degree of heart enlargement. The enlargement by fluoroscopic estimation was arbi-

Table II. *Heart enlargement by the fluoroscopic and teleroentgenographic methods*

Patients		Fluoroscopy			Transverse cardiac diameter			Frontal area		
Decade	Total no.	Actual	Visual estimate	Cardiothoracic ratio ≥50	Actual no.	≥110%	≥115%	Actual	≥110%	≥115
4	27	27	8	7	23	5	3	24	11	4
5	28	28	6	8	26	11	4	27	13	8
6	28	28	12	13	28	8	7	27	17	15
7	22	22	12	10	20	10	4	20	11	9
	105	105	38	38	97	34	18	98	54	36

Actual no. = Total no. – laboratory waste

trarily graded as slight in 31 moderate in 6 and marked in only 1 patient. By the transverse cardiac and frontal area measurements on the roentgenogram only 2 or 3 patients in each decade showed an enlargement greater than 120 per cent.

Electrocardiography By the usual ECG standards[9] there were no patterns of left (or right) ventricular hypertrophy or strain in any of the ECG s in the entire group

As previously reported[1] neither the site of the infarct nor its transmurality (employing the abnormal Q wave as the differentiating criterion) had any influence on survival. The ECG site of infarction did not differ significantly in those with fluoroscopic enlargement and those without (anterior 15 versus 21 posterior 11 versus 29 respectively) As shown in Table III there was an increased incidence of transmural infarction in those with cardiomegaly but in contrast to the Finnish study[2] this did not reach significance

The cardiac rate was similar in those with and without heart enlargement by fluoroscopy The only arrhythmias found in the ECG s consisted of ventricular premature beats which were unifocal single and infrequent. They were significantly more common in the group with fluoroscopic enlargement (9 of 36 versus 4 of 64 $p < 0.01$)

Possible complicating parameters To ensure that the groups with and without heart enlargement were otherwise similar possible complicating parameters were examined The time interval from infarction to entry into study is important, as survival was lower in patients with more recent infarctions.[1] The difference between the two groups was not significant. The mean hemoglobin systolic and diastolic blood pressure height, weight, chest circumference and body build indices were similar in both groups.

The mean age of the patients with heart enlargement proved to be significantly higher (53.5 versus 47.3 years, $p < 0.01$).

Relation of heart size to other parameters The groups with and without fluoroscopic heart enlargement did not differ significantly as to the mean fasting concentrations of serum cholesterol phospholipid, standard S_f lipoprotein fractions and uric acid, and blood sugar

The groups did not differ significantly as to socioeconomic classification, physical activity smoking and intake of calories, fats, and alcohol

Relationship of heart enlargement to survival

A SURVIVAL CALCULATED FROM DATE OF INITIAL EXAMINATION

1 Fluoroscopic visual estimation As seen in Fig 1 the survival curve of the patients with heart enlargement was consistently lower than that of the patients without heart enlargement From the thirtieth month on this was significant ($p < 0.05$) At 5 years, the survival was only 43 per cent versus 78 per cent ($p < 0.001$) and at 10 years 29 per cent versus 50 per cent ($p < 0.05$)

2 Teleroentgenography

Transverse cardiac diameter The survival curves of the 34 patients with a diameter of 110 per cent or more and of the 18 with 115 per cent or more were less consistently but not significantly lower than those of the other patients.

Frontal area The survival curve of the 54 patients with an area of 110 per cent or more was similar to that of the 41 patients below 110 per cent. The survival curve of the 36 patients with an area of 115 per cent or more was consistently but not significantly lower than that of the 61 patients below 115 per cent.

B SURVIVAL CALCULATED FROM DATE OF INITIAL INFARCTION

Table III *Fluoroscopic enlargement and ECG transmurality*

Fluoroscopic group		*ECG infarction*	
		Transmural	*Non transmural*
Without enlargement	50	34	16
With enlargement	30	24	6
Totals	80†	58	22

*Not significantly different.

†Twenty-five ECG' were normal or combined transmural and nontransmural.

MONTHS FROM INITIAL EXAMINATION

68 WITH NO HEART ENLARGEMENT
37 WITH HEART ENLARGEMENT

Fig. 1. The relationship between heart size as determined by fluoroscopic visual estimation, and survival. Heart enlargement denotes any degree. There were no deaths between 109 and 120 months.

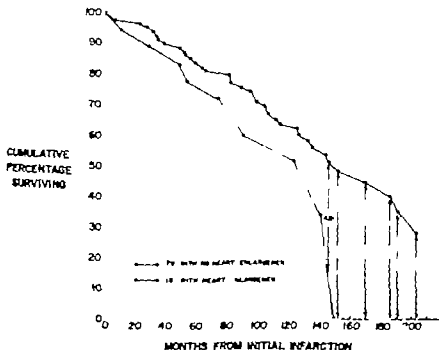


Fig. 2. The relationship between heart size, as determined by the transverse cardiac diameter on the teleoroentgenogram, and survival. Heart enlargement denotes 115 per cent or more.

The results were similar to those calculated from date of initial examination at time of entry into study. When heart enlargement was assessed by fluoroscopic estimation, survival in patients with enlargement was significantly lower after the month no. 115. By the frontal area method a similar trend was observed but did not reach significance. As shown in Fig. 2, survival of the patients with transverse diameter of 115 per cent or more was consistently lower than the patients below 115 per cent and significantly so after the month no. 149.

Discussion

A survey of the literature suggested that the occurrence of heart enlargement following infarction in the absence of complicating conditions remains controversial because previous studies simply were not designed to examine this question.[2] Accordingly, the selection of our clinical material was especially rigid. As well as having unequivocal evidence of myocardial infarction, our CHD patients were free of any other demonstrable condition which could affect the variates to be studied: heart size and survival. Specifically, none of the participants had (1) any other cardiac defect, (2) any noncardiac condition, (3) any evidence of heart failure, and (4) any hypertension (pressure above 150/90 mm. Hg) preceding or following infarction. The availability of previous military documents afforded the unique opportunity to recognize and exclude those coronary patients with normal pressure levels who had hypertension before their infarctions. Because of these highly selected criteria, over 5,000 hospital files classified as "arteriosclerotic heart disease" and "myocardial infarction" had to be reviewed to assemble the 105 coronary patients. The fact that 90 per cent of the deaths were due to CHD further testifies to the stringent selection of the group and to the elimination of other potentially fatal disease.

Heart enlargement includes dilatation (increased cavity size) and hypertrophy (increased weight). Even considerable hypertrophy of the left ventricle increases myocardial thickness only a few millimeters which cannot be discerned by x-ray or fluoroscopy. Heart enlargement that can be demonstrated by these methods usually denotes dilatation of the heart cavity. The ECG remains relatively normal except when the enlargement is accompanied by substantial hypertrophy, which it can detect with greater sensitivity than x-ray methods.[8] In our patients, heart enlargement could be demonstrated by the x-ray methods but not by ECG, suggesting that it was due primarily to dilatation rather than to hypertrophy.

In pulmonary emphysema, cardiac measurements on roentgenograms are significantly smaller than normal but at necropsy the heart weights are normal so that the change in heart size is apparent rather than real.[11] It has long been recognized that even in the absence of complicating conditions, the weight of the heart after infarction is often increased at necropsy.[12] Our own postmortem data on 19 patients with a mean body weight of 1[illegible] pounds showed that as well as dilatation there was a significant increase in the weight of the hearts, the mean value being 455 grams. Thus the clinical demonstration of cardiac enlargement in this group of CHD patients may be accepted as valid. It is interesting to note that this degree of cardiac hypertrophy was not demonstrable by ECG.

From the clinician's viewpoint, the absence of heart enlargement does not, of course, invalidate the diagnosis of myocardial infarction, acute or remote. On the other hand, marked enlargement by x-ray or hypertrophy by ECG should suggest complicating or associated conditions. Waris, Siitonen and Himanka[3] recommended routine radiologic measurement of heart size in the postinfarct patient as a help in prognosis. Our results support their work and extends it to include selected patients without hypertension or congestive failure.

The cause or causes of the enlargement of the heart in CHD remain speculative. Ischemia per se may directly result in cardiac hypertrophy. This is suggested clinically by its occurrence in anemia and in cases of an anomalous coronary artery arising from the pulmonary artery. In the experimental animal the production of coronary atherosclerosis even [illegible]

infarction resulted in an increase in heart weight[14] as did coronary artery ligation.[15]

Heart enlargement following myocardial infarction may involve other mechanisms. Even by indirect evidence acute infarction results in left ventricular failure in two thirds of patients. Recent hemodynamic investigations have demonstrated a spectrum of chronic abnormalities of the left ventricle following infarction. These include poor ventricular contraction, aneurysms, localized or generalized, and mitral regurgitation of varied severity.[17] Our data suggest that even in survivors of myocardial infarction without clinically overt failure appreciable dilatation of the left ventricular cavity occurs in about a third. This in turn stimulates some hypertrophy of the left ventricle with a consequent increase in the heart weight.

Thus in chronic CHD cardiac dilatation (Frank Starling mechanism) and cardiac hypertrophy may compensate for decreased myocardial contractility. Since there was no overt congestive failure these adjustments of the diseased heart can be considered reasonably successful. Unfortunately disease of the myocardium (including that due to coronary obstruction) not induced by excessive pressure-volume loads is often characterized by inappropriate dilatation and hypertrophy.[1] This leads to excessive oxygen consumption relative to ventricular work and low ventricular efficiency.[1] That the compensation in the patients with heart enlargement was not perfect is attested to by their prognosis being worse than that of the patients without enlargement.

Heart enlargement occurred more often in the oldest decade. Possibly, as in all types of heart disease, this represents poorer compensation of the aged heart to any type of insult, cardiac or extracardiac.

It has been demonstrated pathologically that bigger hearts are associated with larger lesions of cardiac necrosis or scarring.[20] In the Finnish study[2] coronary patients with radiologic heart enlargement had more transmural infarction by ECG than did patients without enlargement. Our patients showed a similar trend but it did not reach significance.

Following myocardial infarction survival is not significantly influenced by the presence of demonstrable ventricular aneurysm.[21] In contrast, even the modest heart enlargement found in our patients adversely influenced survival. This again emphasizes the fact that in CHD there are a multitude of factors determining heart size and function and thus prognosis.[17]

In our postinfarct patients, heart size, at least as related to prognosis, was better assessed by fluoroscopy than by the roentgen mensurations. The reason may be simply that fluoroscopy provides a three-dimensional view of the heart, posteroanterior films only a two-dimensional view. Precise measurements of heart chamber volumes and dimensions now have become possible with the advent of biplane cineangiocardiography and soon may prove more important in prognosis.

Summary

One hundred and five men, 30 to 69 years of age, who survived myocardial infarction by at least 3 months and were free of congestive failure, hypertension and conditions influencing heart size or survival were selected. Heart size was determined by ECG, fluoroscopy, and chest x-ray measurements of the cardiothoracic ratio, transverse cardiac diameter, and frontal cardiac area.

ECG failed to reveal any cardiac enlargement. By fluoroscopy or x-ray about 35 per cent of the patients, especially the older ones, did have enlargement of slight to moderate degree. This suggests that the enlargement was due to cardiac dilatation rather than to gross hypertrophy.

In comparison with the patients having normal heart size, the ECG in those with fluoroscopic enlargement did not differ in site of infarction but showed more ventricular premature beats. The patients with cardiomegaly were similar to the other patients in regard to fasting serum lipids, lipoproteins and uric acid, fasting blood sugars, socioeconomic class, physical activity, diet, and use of alcohol and tobacco.

Survival of patients with cardiomegaly was consistently and significantly lower than those with normal heart size: at 5 years, 43 versus 78 per cent ($p < 0.001$); at 10 years, 29 versus 50 per cent ($p < 0.005$). Fluoroscopy gave a better indi-

cation of prognosis than did the x-ray measurements.

In conclusion modest cardiac enlargement is demonstrated by fluoroscopy and x ray but not by ECG in one third of patients with uncomplicated myocardial infarction and it adversely influences long term survival.

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Sudden death in congenital aortic stenosis

A review of eight cases with an evaluation of premonitory clinical features

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Sudden death has been reported to occur in 6 to 19 per cent of children with congenital aortic stenosis.[1-4] In all these series, patients who died suddenly exhibited evidence of severe cardiac disease in one or more ways: (1) symptoms, (2) significant cardiomegaly clinically and/or roentgenologically, and (3) abnormal electrocardiographic findings. Although an abnormal electrocardiogram was recorded in most of the fatal cases, sudden death has been reported to occur in patients with normal electrocardiograms.[1, 4]

This report is an analysis of the experience of the Cardiac Clinic of the Harriet Lane Home and the Children's Medical and Surgical Center of The Johns Hopkins Hospital from 1947 through 1967. An attempt is made to assess the ability of the clinician to anticipate impending disaster in children with congenital aortic stenosis by evaluation of the history, physical examination, chest roentgenogram, and electrocardiogram (ECG).

Methods

This study group was composed of 8 patients with congenital aortic stenosis who died suddenly without any evident precipitating cause other than their underlying cardiac disease. Only one patient (Case 5) was operated upon; however, since the surgery was palliative and had little effect upon his clinical course or findings, he is included in the study. The remaining patients were unoperated because of either failure to recognize in time the severity of the disease (Case 1), inability to obtain parental consent (Case 3), or inadequacy of existing surgical techniques (Cases 2, 4, 6, 7, 8).

The total number of patients at risk in the study (i.e., the number of children with congenital aortic stenosis seen in the Clinic during the period from 1947 to 1967) is unobtainable. However, from November 1961 through December 1967 a total of 199 new patients were diagnosed as having aortic stenosis as the dominant or only

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cardiac lesion 2 of these children died suddenly an incidence of 1 per cent.

Whenever possible each patient was evaluated in terms of several parameters. Clinical criteria included symptoms, systolic thrill exaggerated left ventricular impulse diminished arterial pulses, and narrowed arterial pulse pressures. Chest roentgenograms and fluoroscopy (as described in the records) were reviewed for evidence of increase in cardiac size left ventricular enlargement, left atrial enlargement and prominence and/or tortuosity of the ascending aorta Electrocardiograms were examined for evidence of abnormalities of rate and rhythm frontal QRS axis deviation left ventricular hypertrophy left ventricular systolic overload (LVSO*) and left atrial enlargement. The following voltage criteria of left ventricular hypertrophy were applied (1) sum of SV_1 plus RV_6 greater than 45 mm (2) RAVL greater than upper limits of normal[7] The requirements for left ventricular systolic overload were S-T-segment depression at least 1 mm below the isoelectric line for at least 0 08 second and/or flattened or inverted T waves in V_5 to V_6. The R wave voltage may be normal or increased[8] Left atrial enlargement was indicated by either broad notched P waves in Leads I or V_6 or broad diphasic P waves in Lead V_1

In order to evaluate the significance of the positive findings in the 8 children who died 31 children who were catheterized consecutively for congenital aortic stenosis were studied Since these children were part of a study evaluating the natural history of all degrees of congenital aortic stenosis and therefore were catheterized regardless of the clinical estimate of severity they represent a cross section of patients with aortic stenosis referred to this Center These control data are also used to assess the significance of absent Q waves in the left chest leads in patients with aortic stenosis this ECG finding has been suggested as an indication of systolic overloading of the left ventricle[3] Twelve of these children had mild disease with peak systolic pressure differences across the aortic valve less than 50 mm. Hg 5 were categorized as moderate (Δ P 50 to 79 mm. Hg) and there were 14 patients in the severe group (Δ P greater than or equal to 80 mm Hg)

Electrocardiograms of each of the 31 control patients were examined by one of the authors (R H G) Chest roentgenograms made within one month of the time of cardiac catheterization were interpreted by a pediatric radiologist (J P D) without knowledge of the severity of the stenosis established at cardiac catheterization. ECG's were available for review in only 6 of the children who died One child had a description of an ECG in his chart and one had no record of an ECG Chest roentgenograms were unavailable in 7 of the 8 sudden death patients and the roentgenographic descriptions were taken from the charts in these cases.

Case reports

Case 1 (JHH 64 83 23). E. P was first seen in the Cardiac Clinic on December 19 1958, at the age of 6 2/12 years. A murmur had been heard at one year of age, and the child had been noted by his parents to become short of breath and tire easily On physical examination his peripheral pulses were described as good with blood pressures of 85/60 in the arms and 90/65 mm Hg in the legs. A systolic thrill maximal in the suprasternal notch and palpable over the neck vessels, with a Grade 4/6 systolic ejection murmur Chest roentgenograms were normal The ECG was within normal limits except that Q waves were absent in Leads V[illegible] and V[illegible] (Fig 1). There were no S-T-segment or T wave changes. The diagnosis of congenital aortic stenosis was made.

Three years later the patient was admitted for cardiac catheterization. His parents stated that his functional capacity had decreased considerably over the previous year Physical examination, roentgenograms, and ECG were unchanged from the previous visit. Retrograde arterial left heart catheterization revealed the following data the left ventricular systolic pressure was 190 mm. Hg, and end-diastolic pressure 0 mm. Hg, and end-diastolic pressure 7 mm. Hg aortic pressure was 104 mm Hg systolic, and 80 mm. Hg diastolic the peak systolic pressure difference across the aortic valve was [illegible] mm. Hg The diagnosis of mild-to-moderate [illegible] aortic stenosis was made and the patient was [illegible] structed to continue normal activity but [illegible] strenuous competitive activities.

Although no treatment was instituted, the patient clinical condition improved steadily [illegible] 1962 the patient was able to carry on normal [illegible] [illegible] (while [illegible] strenuous exercise) [illegible] turing His clinical findings remained [illegible] until he was seen on M[illegible] 14 1964 [illegible] noted that the peripheral pulses were d[illegible]

*The term LVSO implies severe left ventricular hypertrophy in response to outflow obstruction we prefer this term to left ventricular "strain."

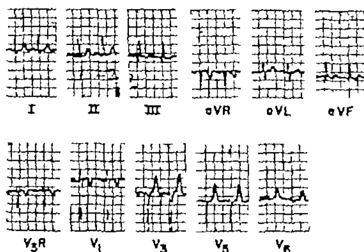


Fig. 1

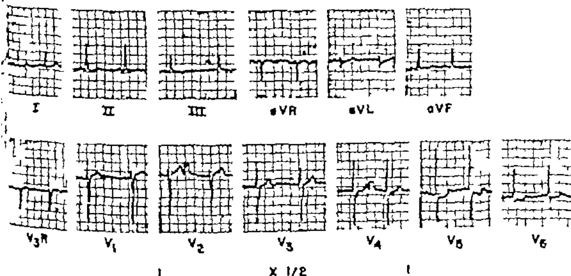


Fig. 2.

palpate. At this time the systolic blood pressure in the arm was 80 mm. Hg the diastolic pressure as unobtainable. An ejection click was described for the first time. Roentgenograms were than normal limits and the ECG was unchanged. However because the patient remained asymptomatic, his parents repeatedly postponed suggested repe t cardiac catheterization.

On J h 1964 the ECG displ ed definite S-T-segment de tion in the right precordial lead suggesting increasing left entricular systolic over loading. Clinical findings were otherwise nchanged An ECG take on March 14 1966, revealed slight S-T-segment depression in Leads V nd V

The patient as seen last on February 2 1967 At this time he as asymptomatic and his parent

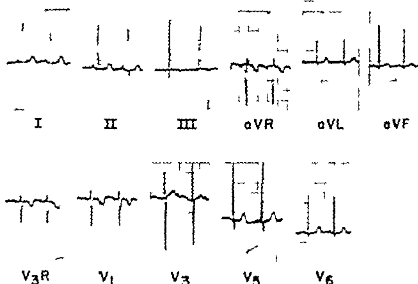


Fig 3

ag n ef ved recatheterization On physical examination, the pulses ere difficult to palpate with blood pressure 80 70 mm. Hg in the arms. Chest films wer unchanged. Although the ECG voltages never exceeded normal lim ts there were definite S-T-segment depressions in Leads V and V and definite S-T-segment elevations in the right chest leads (Fig 3)

The patient died in August, 1967 t the age of 14 10/12 years while in the bathroom at home No utopsy w performed

Case 2 (JHH 49 33 94). D M was first seen in the Cardiac Clinic in May 1952 at age 6 months for evaluation of beart murmur detected at age 3 eeks. Her growth and development had been entirely normal and she had no symptoms referable to the cardiovascular tem. An ECG at this time a essentially w thin normal limits except for the absence of Q wa es in Lead V od V. Additional information from this is t is not a ailable. The diagnosis of ubaortic tenosis as made.

The patient w seen next on March 12 1954 at ge 2 3/12 years shortly after episode that occurred while alking ith her mother She suddenly slumped down her eyes rolled back breathing became irregular and he lost consciousness and became cy notic There no tongue biting tonic-clonic movements or incontinence She re vived after several minutes and howed no further difficulty

When seen in the Cardiac Clinic a few hours after the attack, she wa pale but acyanotic nd in no distress. Good radial arterial pulses were palpable bilaterally the blood pres ure w 100/60 mm. Hg in the left arm and the pulse 110 per minute. There wa thrill over the entir precordium, maximal over the base of the heart nd upper right ternal border and tr smitted w ll into both sides of the neck. The l ngs were clear and the results of neurologic examination were within normal limit

On fluoroscopy the heart as described as being the upper limit of normal in size with no evidence of left or right entricular enlargement, normal left atrium and normal hilar vascularity The ECG revealed a normal sinus rhythm ith a rate of 15 per minute and there were no S-T-segment or T wave changes (Fig 3). Voltage criteria of left ventricular hypertrophy ere not met, and a Q wave was present in Leads V and V Left atrial enlargement was suggested by biphasic P in Lead V with greater positive than negative component. Again the diagnosis of subaortic stenosis was made, but the etiology of the cyanotic, syncopal episode remained unresol ed, although the possibilities of Stokes-Adams attack or convulsion of unknown etiology ere considered.

Seven days later on March 19 1954 the patient was brought to The Johns Hopkins Hospital with what was described as an apneic, cyanotic ep... She was hospitalized in Harriet Lane Home where and ECG wa essentially unchanged from the previous [illegible]. A hythm strip ECG taken during application of persistent pressure t right and the left carotid regions revealed no change in rate. The patient was discharged in good condition after several days.

After being home and ell for several days the patient suffered another episode of unconsciousness and cy nosis, and resuscitation attempts at Baltimore City Hospitals ere unsuccessful. Postmortem examination at Baltimore City Hospitals rev... stenotic, bicu pid ortic alv marked left ventricular hypertroph and chronic passive congestion of the lungs.

Results

Tables I and II summarize the findings in the sudden death and prospective ... fatal groups respectively

Table I. Clinical, radiologic, and electrocardiographic findings in 8 patients with sudden death

			Clinical		Roentgenologic		Electrocardiogram			
Case	Sex	Age at death (yr) and year	Symptoms	Blood pressure pulses	Cardiomegaly*	Large aorta	SV and RV (mm)	QV	Depressed S-T*	T inversion
1	M	14 (1967)	Fatigue, shortness of breath	80/70 pulses small	0	0	42	0	+	0
2	F	2 (1954)	Syncope	100/60	0	0	33	+	0	0
3	F	14 (1966)	Fatigue	90/70 pulses small	+		61	0	+	+
4	F	23 (1957)	Fatigue dyspnea on exertion	100/50	+	?	39	0	+	+
5	M	12 (1953)	Dyspnea on exertion	94/80	+		> 70	+	+	+
6	M	15 (1953)	Fatigue	90/80 pulses feeble	+	+	58	0	+	+
7	M	11 (1948)	None	100/unobtainable pulses feeble	+	+	–	–	–	–
8	M	6½ (1947)	Fatigue, congestive heart failure	60/40 pulses weak	+		–	–	–	–

*Key: + = present; 0 = absent; ? = questionable; – = not available.

Table II. Clinical, radiologic, and electrocardiographic findings in 3 groups of patients with congenital aortic stenosis

	Clinical		Roentgenologic			Electrocardiogram				
Group	Symptoms	Pulse pressure <20 mm. Hg	Cardiomegaly	Enlarged L. vent.	Prominent aorta	SV and RV >45 mm. Hg	SV and RV V >45 mm. Hg	Absent QV V	S-T depression	T inversion
Mild: <50 mm. Hg (12 patients)	0	1	6	9	10	4	9	3	0	0
Moderate: 50 to 79 mm. Hg (5 patients)	0	0	2	3	3	1	3	3	0	0
Severe: ≥80 mm. Hg (14 patients)	5	5	9	10	6	7	13	6	6	8

Clinical findings

SYMPTOMS Of the 31 control patients in our study 5 were symptomatic 2 exhibited easy fatigue one experienced lightheadedness with exertion one suffered 2 episodes of chest pain and one remained dyspneic and in congestive heart failure. All 5 of the symptomatic patients were in the severe category with systolic pressure differences across the aortic valve ranging from 80 to 122 mm Hg Seven of our 8 children who died were symptomatic at some time in their clinical course. The most common symptoms were easy fatiguability and exertional dyspnea One patient (Case 2) died during the third apneic and cyanotic spell Interestingly one patient (Case 1) who had had significant shortness of breath on exertion became asymptomatic about five years prior to his sudden death

PHYSICAL EXAMINATION In our group of 8 patients with sudden deaths, a left ventricular thrust was described in one patient the apical impulse was not described in 4 patients and was reported as normal in 3 patients. A systolic thrill was present in 7 of the 8 fatalities.

In the control group of our study brachial artery pulse pressure equal to or less than 20 mm Hg was found in 5 of 14 patients in the severe category none of 5 in the moderate category and one of 12 in the mild category In 5 of the 8 fatalities in our study the peripheral pulses were described as weak or feeble arterial pulse pressure in these 5 and one other patient ranged from 20 mm Hg to imperceptible (i e no diastolic component was heard) It is interesting that one patient (Case 1) had good peripheral pulses at the time of the cardiac catheterization which revealed a pressure difference of 46 mm Hg across the aortic valve however 3 years later (and 3 years prior to his sudden death) it was noted that the arterial pulses had become difficult to palpate with a blood pressure of 80 70 mm Hg in the arms.

Roentgenologic findings In our control group left ventricular enlargement or generalized cardiomegaly was present radiographically in 9 of 12 patients in the mild category 3 of 5 in the moderate category and 11 of 14 in the severe category Four of the 8 sudden deaths in our study occurred in children who had been reported to have enlarged cardiac shadows, and 2 others were said to have normal heart size but evidence of left ventricular enlargement.

Abnormal radiologic appearance of the aorta was frequent in all the control patients in our study with a prominent or tortuous aortic contour in 10 of 12 patients in the mild category 3 of 5 in the moderate group and 6 of 14 in the severe group. Of our 8 patients with sudden death, 2 were described as having an enlarged aortic knob 2 had an aortic knob of normal contour and in 4 the aortic knob was not described In addition 2 were said to have roentgenographic evidence of left atrial enlargement (one slight) 3 had a normal left atrium and 3 had no mention of atrial contour

In our study chest films were of little help in assessing the severity of congenital aortic stenosis

Electrocardiographic data In our study neither the 31 control patients nor the 8 patients who died suddenly had abnormalities of rhythm or conduction on ECG The frontal QRS axis was definitely leftward in 2 of the patients with sudden death suggestively leftward in 2, normal in 3 and unreported in one In none of the 8 children who died was there demonstrated convincing electrocardiographic evidence of left atrial enlargement

Analysis of electrocardiograms according to several criteria is shown in Table III Voltage standards for left ventricular hypertrophy and the absence of Q waves in Leads V_5 and V_6 were of no help in the assessment of severity Only left ventricular systolic overload was significantly more common with increasing severity In our control group of 31 none of the 17 patients with mild or moderate stenosis exhibited LVSO while 8 of 14 patients in the severe group displayed unequivocal evidence of LVSO and 2 more had suggestive T wave changes. LVSO was present in 5 of the 6 electrocardiograms of patients with sudden death In 2 of these patients evidence of LVSO was absent initially and appeared or persisted after they were said to be asymptomatic. The one child (Case) who died without S-T-segment or T-wave changes also did not meet usual voltage

Table III. Comparison of electrocardiographic criteria of left ventricular hypertrophy

Criterion	Reference	Mild (12 patients)	Moderate (5 patients)	Severe (14 patients)	Sudden deaths (6 patients)
LVSO*	8	0	0	8	5
Absent QV₅, QV₆	10	3	3	6	4
SV₁ plus RV₅ >45 mm.	23	4	1	7	3
SV₁ plus RV₅ >35 mm.	—	2	0	2	3
SV₁ or SV₂ plus RV₅ or RV₆ >45 mm. Hg	24	9	3	13	4
RAVL > upper limits of normal	24, 7	—	—		1

*Chi square = 4.21; <0.05 for mild, moderate, and severe.

criteria for left ventricular hypertrophy (SV_1 plus RV_5 greater than 45 mm.); however, the R/S ratio in the right chest leads was less than lower limits of normal and her symptoms (apneic, cyanotic, syncopal attacks) were dramatically suggestive of grave cardiovascular pathology.

Discussion

Sudden death occurs infrequently in congenital aortic stenosis (Table IV). It is important, however, to detect patients with severe stenosis, since they are most susceptible to catastrophe. Because cardiac catheterization which would be part of the presurgical evaluation is not without morbidity and even slight mortality rates,[4] it seems unwise to catheterize indiscriminately all patients with congenital aortic stenosis. Accordingly, it is important to learn which clinical criteria are most sensitive and reliable in pointing out which children have severe congenital aortic stenosis.

Exertional dyspnea, syncope, chest pain, or fatigue are grave prognostic signs in patients with congenital aortic stenosis and rarely occur except with severe stenosis.[11] Symptoms are found in a high percentage of patients who die suddenly with this disease (Table V). The 5 patients with symptoms in our nonfatal group all had peak systolic pressure differences across the aortic valve greater than 79 mm. Hg. Seven of our 8 fatalities were symptomatic at some time in the course of their illness.

Braunwald and associates[11] reported that 87 of 100 consecutive patients with con-

Table IV. Incidence of sudden death in congenital aortic stenosis

Author	Total with aortic stenosis	Sudden death	Per cent
Marquis and Logan, 1955	28	5	19
Downing, 1956	37	3	8
Braverman and Gibson, 1957	85	6	7
Morrow et al, 1958	30	2	7
Ongley et al, 1958	6	4	6
Peckham et al, 1964	30	4	13
Campbell, 1968	87	8	9
Glew et al, 1969	199	2	1

genital aortic stenosis had a prominent left ventricular impulse; the 13 exceptions were among 17 patients whose systolic pressure differences were 25 mm. Hg or less. In the same study, all 15 patients in whom a precordial systolic thrill could not be felt had pressure differences across the aortic valve of less than 30 mm. Hg. Peckham and associates[3] reported that in their group of 300 patients, 17 of 12 patients with pressure differences across the aortic valve of less than 35 mm. Hg had no thrill, while all 4 of their patients with sudden death had a systolic thrill and a pronounced left ventricular thrust. Therefore, lack of a left ventricular thrust and systolic thrill almost invariably indicates mild obstruction. However, the presence of these findings in a

Table V Occurrence of symptoms in sudden death

Author	*N of sudden deaths*	*Asymptomatic*	*Symptomatic*	*Fatigue*	*Dyspnea, shortness of breath*	*Syncope*	*Angina*	*Congestive heart failure*
Glew et al., 1969	8	1	7	5	3	1	0	1
Campbell, 1968	5	0	5	0	4	3	2	0
Reynolds et al 1960	2	0	2	0	0	1	2*	0
Ongley et al. 1958	4	1	3	2	2	0	0	0
Morrow et al.[12] 1958	2	0	2	2	1	0	1	0
Braverman and Gibson, 1957	6	2	4	2	0	3	0	0
Kjellberg,[13] 1955	1	0	1	1	1	0	1	0
Marquis and Logan, 1955	5	0	5	0	0	1	0	2
Totals	33	4	29	12	11	9	4	3

*Acute, severe abdominal pain without evident pathology; thought to be manifestation of severe aortic stenosis.

patient with congenital aortic stenosis gives no further indication of the severity of the stenosis.

Peckham and associates[3] concluded that a decreased peripheral arterial pulse pressure (less than 25 mm Hg in the brachial artery) is a sign of significant (moderate to severe) obstruction. In our study brachial artery pulse pressure of less than 20 mm Hg was found in 36 per cent of the living patients with severe aortic stenosis and in 63 per cent of the patients with sudden death but in only 6 per cent of the patients with mild and moderate stenosis.

No correlation has been reported between cardiac size or contour including aorta and left ventricle and severity of stenosis.[1,12] In our study roentgenologic examinations similarly were of no assistance in evaluating the severity of the aortic stenosis.

Electrocardiogram It is widely believed that the electrocardiogram is a reliable and sensitive yardstick for assessing clinically the severity of congenital aortic stenosis.[3-4] Hancock and Fleming[12] reported good correlation between the degree of obstruction and precordial voltages and T wave inversion In the report by Ongley and associates[4] their 4 sudden deaths (excluding one death from a ruptured left subclavian aneurysm) all occurred in children with left ventricular hypertrophy on ECG in addition 3 had T wave changes and 2 exhibited S-T-segment and T wave abnormalities suggestive of LVSO Marquis and Logan[8] reported that only 1 of 5 patients died without developing inverted T waves in the left chest leads they concluded that ECG evidence of left ventricular hypertrophy particularly with evidence of LVSO is the most reliable sign of severe congenital aortic stenosis. Peckham and co-workers[3] reported that of 5 cases of sudden death in patients with congenital aortic stenosis, 3 had an ECG pattern of LVSO while the fourth had complete left bundle branch block. Of 40 patients with pressure differences across the aortic valve greater than 50 mm Hg 39 exhibited left ventricular hypertrophy 24 of these with evidence of LVSO (inverted T waves in the left precordial leads) one patient had a normal ECG

On the other hand several authors[1,4,12] have reported normal electrocardiograms in cases of severe or fatal congenital aortic stenosis. Nadas[14] states that 25 per cent of patients with severe aortic stenosis have either normal electrocardiograms or only voltage signs of left ventricular hypertrophy In the study by Hugenholtz and associates[15] in 22 per cent of patients with peak systolic pressure differences (across the aortic valve) greater than 100 mm Hg there were no S-T-segment or T wave changes. Furthermore these authors re-

ported that their group had seen 11 patients with "high-grade" aortic stenoses who had normal electrocardiograms. Jones and associates[11] reported that 50 per cent of their patients with severe aortic stenosis had normal electrocardiograms. However in their study if only voltage criteria of left ventricular hypertrophy were met or if S-T-segment changes were questionable the ECG was regarded as normal. Two of the 6 sudden deaths in the children reported by Braverman and Gibson were said to have had normal electrocardiograms. Reynolds and co-workers[6] reported 7 patients with severe congenital aortic stenosis without S-T-segment or T wave changes or definite left ventricular hypertrophy on the electrocardiogram. However examination of the two electrocardiograms illustrated in their report reveals abnormal features. In both cases the ECG evolves towards left ventricular hypertrophy with RV plus SV_4 exceeding 45 mm late in Case 2 and R waves disappearing in V in both patients and suggestive S-T-depression appearing in the left precordial leads in Case 1.

Braunwald and associates in a study of 100 patients, reported that there was no significant correlation between peak systolic pressure difference (or left ventricular systolic pressure) and mean frontal QRS axis, the ratio of R/S in Lead V or the sum of RV and SV_1. However in patients younger than 10 years of age there was moderately good correlation of RV and SV_1 with severity of the stenosis. Only gross correlation existed between the severity of the stenosis and the T wave in the left precordial leads, i.e., no patient with pressure difference greater than 110 mm Hg had an upright T wave although upright T waves were seen in patients with pressure differences up to that value.

In our control group S-T-segment and T-wave changes indicative of LVSO were present in 71 per cent of the severe cases and in none of the mild or moderate cases. In addition 5 of the 6 patients with sudden death with electrocardiogram exhibited LVSO. Hence although some patients with grave congenital aortic stenosis [illegible] impressive electrocardiogram [illegible] tients in this category exhibit [illegible] cardiographic abnormalities [illegible] left ventricular syst[illegible]

In the present study the absence of Q waves in the left precordial leads was so frequent in all patients, particularly those with at least moderate stenosis that this finding was of no help in assessing severity. Absent Q waves in V_5 and V_6 may be an early sign of left ventricular systolic overloading since it is found in a fair proportion of even mild cases of aortic stenosis. Our results also indicated that voltage criteria of left ventricular hypertrophy are unreliable in the evaluation of severity.

Vectorcardiogram. In recent years the vectorcardiogram has been supported as a more sensitive and reliable tool than the scalar electrocardiogram in the evaluation of the severity of congenital aortic stenosis. Hugenholtz and Gamboa and Gamboa and associates[1] reported a close correlation between the maximum spatial vector in the Frank lead system and left ventricular peak systolic pressure in 50 patients with congenital valvar aortic stenosis; they concluded that this correlation could be useful in the assessment of the severity of the stenosis. Subsequent investigators have failed to confirm this relationship.[19] In addition Hugenholtz and Gamboa[7] reported less significant correlation between the maximum spatial vector and pressure difference across the aortic valve, valve area, or stroke work, perhaps due to the greater laboratory errors associated with these latter measurements. However this could be because the elevated left ventricular systolic pressure in aortic stenosis is the main factor affecting the maximum spatial vector[7] or because this vectorcardiographic measurement is not related in simple fashion to mechanical phenomena in the heart.[1] In any case the value of the vectorcardiogram in the evaluation and follow-up of patients with congenital aortic stenosis remains to be proved.

[illegible] congenital aortic stenosis. An important aspect of this study [illegible] in [illegible] severity of the aortic stenosis in Case [illegible] following the disappearance of symptoms after catheterization which revealed only mild valvar aortic stenosis, the patient developed markedly narrowed [illegible] and LVSO [illegible] after catheterization [illegible] possible explanation

First the catheterization data were incomplete since cardiac output was not measured and the cardiac output may have been low at this time thus minimizing the measured systolic pressure differences.[8] Second the patient's aortic valve was essentially of fixed orifice size so that his general body growth outstripped any increase in valve area Third it is possible that his aortic valve underwent organic modification such as calcification or infective endocarditis which worsened the degree of stenosis No postmortem examination was performed and the mechanism underlying his deterioration and death remains speculative

Summary

Sudden death in patients with congenital aortic stenosis is a rare but dramatic event. Only 8 sudden deaths occurred in a 20 year period in our clinic an incidence of 1 per cent (from 1961 to 1967) It is even less common for sudden death to occur in the absence of one or more warning symptoms or signs Therefore death in congenital aortic stenosis may be sudden but it should not be unexpected

In severe cases of congenital aortic stenosis the electrocardiogram usually exhibits S-T segment and T wave changes of left ventricular systolic overload Although severe cases infrequently may have a normal electrocardiogram it is extremely unlikely that such a patient would not have some other indication for cardiac catheterization Our criteria for cardiac catheterization are the presence or appearance of symptoms referable to the cardiovascular system narrowed peripheral arterial pulses or LVSO on electrocardiogram

Even mild cases of congenital aortic stenosis may progress and all patients require careful extended follow-up with sequential physical examinations and electrocardiograms Repeat cardiac catheterization must be performed whenever changes in symptoms or signs warrant it

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Absolute hemodilution cardiopulmonary bypass: Free water distribution and protein mobilization in body compartments

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Intentional hemodilution is widely used in cardiac surgery. Many complications formerly encountered when heart-lung machines were primed entirely with whole blood have been reduced or eliminated with diluted perfusate. However, hemodilution methodology in different institutions varies so much that neither the physiologic alterations induced by it nor the actual limits of its clinical safety are well defined.

Attempts to analyze accounts of physiologic and hemodynamic responses to hemodilution are frustrated by inconsistencies in experimental design and extrapolation of the results of animal investigations to clinical situations. Knowledge about the following is necessary for properly assessing the effects of hemodilution: (1) composition of the pump-oxygenator prime, (2) type and duration of bypass, (3) the patient's preoperative clinical state, and (4) characteristics of fluids for replacing blood loss. Publications on hemodilution often carry just fragmentary particulars about these variables. In the absence of such information, evaluation of the efficacy or safety of any given diluent or method is insecure.

Most documentation on hemodilutive practices has focused on observed clinical benefits, and on the extent to which different gradations of anemia are tolerated. Of greater fundamental importance to the understanding of hemodilution would be a description of the manner in which the organism copes with the large quantity of nonhemic fluids which it receives from the combined prime and assorted intravenous medications. Interpretation of data from previous studies on fluid shifts in body compartments due to hemodilution is hindered by considerations about blood administered during or after cardiopulmonary bypass.

A unique opportunity for examin...

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Table I. Clinical particulars

Patient	Age sex diagnosis	N. Y. Heart Assoc. Classif	Height weight blood volume	Procedure	Anesthesia time, operating time, bypass time	Clinical result
1	20 F; ASD and anomalous drainage of SVC to LA	II C	5 ft. 2 in. 42.6 Kg 3.5 L.	Suture ASD and relocate SVC to RA	6 hr 15 min. 5 hr 1 hr 10 min.	Improved
2	47 F AI from ruptured left coronary cusp	III C	5 ft. 3 in. 52.7 Kg 4.2 L.	Aortic valvoplasty with fascia lata	8 hr 30 min. 8 hr 1 hr 23 min.	Fatal cerebral embolism 2nd postoperative day
3	55 M; posttraumatic MI and MS	III C	5 ft. 10 in. 60.9 Kg 4.9 L.	Mitral valvoplasty with fascia lata	7 hr 50 min. 7 hr 2 hr 26 min.	Improved
4	26 F rheumatic MI	II C	5 ft. 4 in. 61.8 Kg 4.4 L.	Mitral valvoplasty with fascia lata	10 hr 35 min. 9 hr 25 min. 2 hr 4 min.	Improved
5	43 F rheumatic MS	II C	5 ft. 1 in. 54.5 Kg 3.6 L.	Mitral valvoplasty	7 hr 5 min 6 hr 45 min. 1 hr 17 min.	Improved

AI = aortic insufficiency; ASD = atrial septal defect; LA = left atrium; MS = mitral stenosis; AS = aortic stenosis; SVC = superior vena cava; MI = mitral insufficiency.

retention and distribution of free water with hemodilution cardiopulmonary bypass presented itself in the instance of cardiac operations performed upon five Jehovah's Witnesses. These subjects did not receive transfusion because of religious objections. For four of them blood replacement during surgery was with crystalloid solutions exclusively. The other was given additionally a small amount of colloid plasma expander. This communication reports and interprets physiologic measurements made in this select group of patients.

Materials and methods

Table I summarizes relevant clinical details about the four women and one man who were studied. The age range was from 20 to 55 years. All had advanced valvar disease, except one who had a large ostium secundum atrial septal defect with an anomalous superior vena cava. Total operating time was between 5 hours and 9 hours 25 minutes. Total perfusion time was between 1 hour 10 minutes and 2 hours 26 minutes. Observations were made (A) immediately before operation, (B) at the conclusion of operation, immediately after transfer of the patient to the intensive care unit, and (C) on the first postoperative day, about 18 hours after operation.

Body weight was recorded with a bed balance sensitive to 1 Gm. All tubing, linen, dressings, and other accessories connected to the patient were weighed separately to provide as accurate a measure of the subject's nude weight as possible.

Total blood volume was measured by means of isotope tracers (R.I.S.A.) and the large vessel hematocrit value was corrected for plasma trapping.

Fluid intake and output were charted meticulously. The fluids administered through the pump-oxygenator and by venoclysis consisted of varying amounts of lactated Ringer's (Hartmann's) solution, 5 per cent glucose in water, thromethamine (THAM), mannitol (Table II), and small quantities of heparin, curare, and pentobarbital. Dextran was given on a single occasion during bypass (Patient 3).

Cardiopulmonary bypass was accomplished with a single-pass pump-oxygena

*Metabolic Scale, Brooklyn Instrument Company, White Plains, N. Y.

Table II Fluids administered in operating room

Patient	I.V. to heart-lung machine*		I.V. venoclysis		Total (ml.)
	Fluid	Amount (ml.)	Fluid	Amount (ml.)	
1	L.R	800	L.R	1 550	
	G/W	300	G/W	200	
	THAM	200	Mannitol	100	3 246
	I.V. drugs	6	I.V. drugs	90	
2	L.R	750	L.R	2 198	
	G/W	350	Mannitol	251	
	THAM	300	THAM	250	4 177
	I.V. drugs	6	I.V. drugs	70	
3	L.R	2 500	L.R	3 500	
	G/W	250	G/W	1 250	
	THAM	300	Mannitol	250	
	I.V. drugs	23	(LMW dextran)	500	8 073 (and 500 ml LMW dextran)
4	L.R	1 000	L.R	4 500	
	G/W	250	G/W	1 500	
	THAM	500	Mannitol	200	7 958
			I.V. drugs	8	
5	L.R	2 500	L.R	3 500	
	G/W	300	G/W	750	
	THAM	400	THAM	150	
	I.V. drug	11	Mannitol	200	7 611

L.R. = lactated Ringer (Hartmann's) solution; G/W = 5 per cent glucose in water solution; THAM = [illegible]; LMW = low molecular weight.

*Volumes indicated represent initial pump-oxygenator prime plus supplementary fluid given by this route during operation.

tor The amount of prime volume employed in individual cases was governed by the patient's preoperative blood volume and hematocrit. Generally attempt was made to lower the hematocrit to approximately 27 per cent after mixture of the prime with the patient's blood volume.

The volume and composition of venoclyses during and after operation depended principally on individual fluctuations in urine output and blood pressure. Colloid plasma expanders were generally avoided because of the associated bleeding tendency.[4]

Preoperative insensible water loss measured by means of the metabolic scale varied between ½ and 1 ml. per minute. However during the surgical procedure it was doubtless higher because of exposure of the thoracic viscera to ambient air and the heat generated by the operating room lights.

Plasma proteins were measured by ammonium sulfate fractionation.

Extravascular fluid changes were estimated as the difference between total fluid retention (weight change) and intravascular retention.

Calculations

In the following formulas, the hematocrit is always expressed as a decimal fraction, i.e., 0.405 rather than 40.5 per cent. Also, the subscript 1 refers to preoperative values, the subscript 2 refers to the immediate postoperative values, and the subscript 3 refers to 18 hour postoperative values.

Formulas

I Corrected hematocrit (decimal) = Ht = large vessel hematocrit (decimal) × F

II Corrected blood volume* (liters) = BV = blood volume (liters) × $\frac{1 - H}{1 - (0.91)}$ ... [illegible]

III Red cell mass (liters) = RCM = BV × H

*For plasma trapping.
†Large plasma-distributed tracer.

Table III *Fluid changes during operation*

Patient No.	Volume administered (ml.)	Volume retained: Ml	Volume retained: %	Volume excreted (urine) (ml.)	Blood loss (ml.)	Weight gain (Gm.)
1	3 246	2 900	89 34	650	640	2 260
2	4 177	2 712	64 92	1 938	2 062	650
3	8 573	5 591	65 21	2 422	2 384	2 707*
4	7 958	4 831	60 70	2 700	1 945	2 886
5	7 611	6 430	84 48	1 930	1 699	4 731
Average	6 313	4 492	72 90	1 928	1 746	2 646
S.D.	2 422	1 641	12 97	786	665	1 461

S.D. standard deviation throughout all tables.
*Includes 500 ml. low molecular weight dextran.

IV Plasma % volume (decimal) = Plcrit = 1.00 − Ht_e

V Plasma volume (liters) = PlV = Plcrit × BV_e

VI. Calculated blood loss (during operation)

$$\text{(liters)} = CBL_4 = \frac{RCM - RCM}{Ht_e}$$

VII Calculated plasma loss (during operation) (liters) = $CPlL_4$ = CBL_4 × Plcrit

VIII. Measured total protein content of plasma (preoperative) (grams) = MTPCP = BV_e × 10 × $Plcrit_1$ × plasma protein concentration in Grams per 100 ml.

IX. Expected total protein content of plasma (postoperative) (grams) = ETPCP = MTPCP − ($CPlL_4$ × 10 × plasma protein concentration in Grams per 100 ml.).

X. Estimated protein mobilized (postoperative) (grams) = EPM = MTPCP − ETPCP

Sample calculations using data in Table I

A. FOR IMMEDIATE POSTOPERATIVE TIME.

RCM = 3 01 × 0.273 = 0.822 L.

$Plcrit_1$ = 1.00 − 0.273 = 0.727

PlV = 0.727 × 3 01 = 2.188 L.

$$CBL_4 = \frac{1\,463 - 0.822}{0.375} = 1\,709 \text{ L.}$$

$CPlL_4$ = 1 709 × 0.625 = 1.068 L.

MTPCP = 3 01 × 10 × 0.727 × 4 92 = 107 66 Gm.

ETPCP = 178.43 − (1.068 × 10 × 7.32) = 100.25 Gm.

EPM = 107 66 − 100.25 = 7 41 Gm.

(Note These figures calculated from average values may differ slightly from those calculated for individual patients and subsequently averaged as in the tables.)

Results

Table III summarizes the blood and fluid changes during operation. The average blood loss was 1 746 ml representing 45 per cent of the average circulating blood volume. The combined volume of heart lung machine and venoclysis fluid averaged 6,313 ml of which 1 928 ml or 31 per cent was excreted as urine The average whole body retention of fluid was estimated at 4 492 ml. It should be recalled that the volumes of fluid administered retained and excreted were separately and independently evaluated. However the average volume of total distributed fluid agrees with that of administered fluid to within 2 per cent. The mean body weight gain of 2 646 Gm was associated with an average fluid retention of 4 492 ml Assuming a specific gravity of 1 0 for fluid retained the difference between these two numbers is 1,846 Gm This approximates the average blood loss figure of 1 746 ml. which was also estimated by independent means.

It therefore appears that during operation for each volume of blood lost, 3½ volumes of nonhemic fluid had to be given to maintain cardiovascular stability Seventy three per cent of the nonhemic fluid administered was retained Hence for each volume of blood lost 2⅗ volumes of crystalloid solution were retained in the body

Table IV outlines the distribution of the retained fluid An average of 815 ml was distributed to the intravascular compartment during operation representing 18 7 per cent of the retained fluid The other 81.3 per cent was distributed to the extravascular spaces. Thus, for each ½ volu

Table IV Partition of retained fluid during operation

Patient No.	Total retention (ml.)	I.V. retention		E.V. retention (ml.)	Replacement of I.V. loss by L.R.* (% of blood lost)
		Ml.	%		
1	2 900	440	15 17	2 460	65 8
2	2 712	682	25 14	2 030	33 1
3	5 591†	1 534†	27 43	4 027	64 4†
4	4 831	806	16 68	4 025	41 4
5	6 430	617	9 59	5 813	38 3
Average	4 492	815	18 74	3 671	48 8
S D	1 641	422	7 39	1 499	16 5

I.V. = intravascular and E.V. = extravascular throughout all tables.
*L.R. = lactated Ringer solution.
†Includes 500 ml. low molecular weight dextran.

Table V Fluid changes 18 hours post-operatively

Patient No.	Volume administered (ml.)	Volume retained		Urine volume excreted (ml.)	Blood loss (ml.)	Weight gain (Gm.)
		Ml.	%			
1	2 191	1 640	74 83	863	310	1 19[illegible]
2	2 670*	560*	20 97	1 964	0	56[illegible]
3	4 850†	1 566†	32 28	3 400	70	1,30[illegible]
4	5 658†	3 249†	42 42	4 893	0	3 2[illegible]
5	4 095	1 947	47 54	2 587	291	1 45[illegible]
Average	4 292	1 792	43 56	2 741	134	1 67[illegible]
S.D	2 165	966	20 21	1 518	154	9[illegible]

S.D. = standard deviation.
*Includes 500 ml. low molecular weight dextran.
†Includes 500 ml. dextran 70.

Table VI Partition of retained fluid 18 hours post-operatively

Patient	Total retention (ml.)	I.V. retention		E.V. retention (ml.)
		Ml.		
1	1 640	360	21 95	1,28[illegible]
2	560	780*	139 28	−25[illegible]
3	1 566†	630†	40 22	934
4	3 249†	649†	19 97	2 60[illegible]
5	1 947	202	10 37	1 31[illegible]
Average	1 792	524	46 36	1 265
S D	966	236	33 04	1 04[illegible]

*Includes 500 ml. low molecular weight dextran for 3 hours preceding study
†Includes 500 ml. dextran 70.

Table VII. *Blood changes*

Patient	*Corrected hematocrit* (%)			*Corrected blood volume* (*liters*)			*Plasma protein* (*Gm.*)			*Estimated protein mobilized* (*Gm.*)	
	Before operation	*End of operation*	*18 hr after operation*	*Before operation*	*End of operation*	*18 hr after operation*	*Before operation*	*End of operation*	*18 hr after operation*	*End of operation*	*18 hr after operation*
1	40 3	34 5	30 5	3 25	3 05	3 10	7 1	5 6	5 2	1 20	11 43
2	31 0	23 0	19 0	4 02	2 64	3 42	7 4	5 9	5 2	19 97	−5 85
3	38 3	22 8	19 5	4 64	3 79	4 35	7 3	3 9	4 2	12 57	35 12
4	34 0	25 3	22 0	4 20	3 15	3 72	7 2	4 5	5 7	−5 55	59 53
5	44 0	31 0	28 3	3 41	2 42	2 34	7 6	4 6	4 3	4 24	4 40
Average	37 52	27 32	23 86	3 90	3 01	3 39	7 32	4 90	4 92	6 49	20 92
S D.	5 12	5 20	5 24	0 57	0 52	0 74	0 19	0 82	0 64	9 94	26 32

of fluid retained in the body ½ volume was distributed intravascularly.†

The next period of observation spans the first 18 hours post-operatively. During this time, blood loss was comparatively negligible. Also during this interval the brisk flow of urine decreased.

The total infusion (average 4,292 ml.) required to sustain a satisfactory arterial blood pressure during this period reflects an increased pace of fluid administration. This resulted in an average of 1 792 ml. of fluid being retained. An average of 46.3 per cent of this quantity was distributed to the intravascular compartment, and the remaining 53 7 per cent to the extravascular spaces (Tables V and VI)

Such an "average" value is misleading however inasmuch as it is derived from individual values which have resulted from at least three physiologically different mechanisms. Thus, Patients 2 3 and 4 constitute a group who received 1 unit each of colloid expander. Further this group is not homogeneous in that in Patient 2 the intravascular volume was reconstituted partly by mobilizing extravascular fluid. For this group the volume of colloid represents 9 9 per cent of the total infusion volume during this period. However excluding Patient 2 there is no striking difference in the intravascular distribution of retained fluid between that group which received colloid and that which did not.

Allied blood changes are summarized in Table VII. By the end of operation the average measured blood volume had fallen by approximately 900 ml.—23 per cent of the average blood volume. The degree of hemodilution which occurred during this period is reflected in the decreased absolute hematocrit value of 27 per cent. This value corresponds to a 27 per cent drop in the preoperative hematocrit but, combined with the stated blood volume figures, it effectively constituted a loss in red cell mass of about 44 per cent. During the second period of observation—the first 18 hours post-operatively—a partial restoration of blood volume was accomplished by intravascular retention of administered fluid resulting in a further decline of hematocrit value to 23.8 per cent.

The data are consistent with the possibility that protein was mobilized to the intravascular compartment from extravascular sources. This possibility was suggested by the finding that after blood loss the "total measured protein content of plasma" exceeded the "expected total protein content of plasma" (see example in Calculations section.) The average estimated protein mobilized during the first

*More precisely 0.47 volumes.

†While Patient 3 received 500 ml. of low molecular weight dextran during operation, this amount constituted only 1.4 per cent of the total infusion given to the 5 patients and may be viewed as free water without appreciably altering the calculations.

interval was 6 49 Gm and during the second interval was 20 9 Gm.

Discussion

This communication concerns the manner in which five cardiotomy patients coped with large quantities of crystalloid fluid administered in connection with hemodilution cardiopulmonary bypass. Observations regarding retention and partitioning of administered fluid cover two intervals the operative period and the first 18 hours after operation Separate and independent estimations of volume administration whole body retention intravascular retention urine volume excretion and blood loss were made Extravascular retention of fluid was calculated as the difference between whole body retention and intravascular retention

The patients were of the Jehovah's Witness faith No blood was administered One patient received 500 ml of low molecular weight dextran during operation The same patient and two others received 500 ml of plasma expander in the second period of observation

During operation the five patients received an average amount of fluid equal to 1 6 times their blood volume to replace a blood loss of 45 per cent of blood volume 73 per cent of the fluid administered was retained The remaining 27 per cent was lost by urination and insensible perspiration An average of 18 7 per cent of the retained fluid was distributed to the intravascular compartment The remaining 81 3 per cent was assigned to the extravascular spaces.

In other words on the average for each volume of blood lost 3½ volumes of nonhemic fluid were administered of which 2⅓ volumes were retained in the body and of which about ½ volumes were retained in the intravascular compartment

In terms of intravascular volume expansion the crystalloid fluid administered was markedly inefficient. The intravascular space received an average of only 13 per cent of the administered fluid or only 19 per cent of the retained fluid Indeed urine excretion amounted to 2⅗ times the intravascular increment.

The above calculations are based on the assumption that 500 ml. of low molecular weight dextran administered to one of the six patients resulted in a relatively insignificant error (1 6 per cent)

Similar group calculations for the second interval of observation—the first 18 hours after operation—are not possible since the patients no longer constituted a similar group.

Closer examination of the information in the tables reveal several instructive differences and similarities which related to physiologic mechanisms.

Patient 2 was the only one in the series who died She received the lowest volume of fluid in relation to blood loss for the operative period as well as for the total observation period. Further she is the only patient in whom extravascular fluid was mobilized to replenish in part, the intravascular volume during the 18 hour postoperative period

Patient 1 lost the least blood, received the least fluid had the highest percentage retention of fluid and mobilized the least quantity of protein during operation.

Patient 3 the only patient receiving colloid in the operative period, had the highest blood loss, received the largest volume of fluid and showed the second highest protein mobilization during operation.

Finally in the postoperative period, Patients 2 3 and 4 as a group exhibited the lowest total retention of administered fluid as well as the lowest retention of fluid intravascular Associated with this is the observation that they excreted the largest volumes of urine. In fact these are the reasons colloid expander solution was administered It appears that the loss of intravascular fluid through the kidneys and the capillaries was most pronounced in this group explaining the need for colloid solution to maintain intravascular volume.

We and others have reported partition ratios between the extravascular and intravascular compartments of 3 1 to 4 1 in blood loss replacement studies with crystalloid fluids[3-7] This is in agreement with the partition ratios calculated for the average values in this study for the operative period of 4 1 However individual partition ratios varied from 3 1 to 9 1 In fact, three of the five ratios were in excess of 4 1

It is possible that the explanation of this difference resides, to some extent in the

effects of the cardiopulmonary bypass procedure These effects could include non pulsatile flow lower mean pressures, decreased renal function expansion of intravascular volume mechanical trauma to the blood creation of new body spaces due to surgical dissection and many others. Some or all of the above could result in physiologic alterations leading to increased fluid extravasation to the extravascular spaces.

Renal function was a highly significant factor in the clinical management of the patients in the study and perhaps also in the fluid distribution to their different body compartments. In general, three distinct periods of renal activity were manifested by these patients. During the first period (cardiopulmonary bypass) urine output usually equaled or was significantly greater than that of the antecedent period During cardiopulmonary bypass, however the systemic pressure was controlled by deliberately varying the flow rates of the extracorporeal pump. Immediately after cardiopulmonary bypass without pump support, blood pressure was stabilized by administration of fluid and the patient was permitted to function on his own with pulsatile blood flow and increased mean blood pressure. This initiated the next interval of renal activity The urine output generally rose remarkably to rates which at times were four to tenfold that of the bypass period The pace of mobilization of fluid from extravascular pools apparently did not compensate for the rapid loss of intravascular volume by urination since hypotension rapidly ensued unless more fluid was added to restore the intravascular volume. In the particular case of the patients studied here fluid supplementation could not be with whole blood or even plasma. Artificial colloid expanders were used sparingly or not at all for fear of inducing an hemorrhagic diathesis. Consequently lactated Ringer's solution was titrated to preserve at least a minimally adequate blood pressure. Thus second period of renal activity—the first few hours post-operatively—was of critical importance requiring the most careful and knowledgeable monitoring The end phases of the second period were characterized by the ability of the patient to maintain a minimally adequate blood pressure in the absence of marked diuresis. This, of course reflected a new status with respect to renal activity The diluted plasma was accepted (or at least not concentrated as ordinarily) by the kidney The third period was characterized by a stable blood pressure and urine output which was near normal reflecting the type and amount of intravenous fluid regimen employed

Certain other observations appear noteworthy Pulmonary edema was not a regular or normal consequence of the massive hemodilution Pleural effusion however was prevalent requiring repeated aspiration in the postoperative period Acidosis and hypokalemia were frequently observed during surgery and required careful monitoring and treatment Hemostasis did not become impaired except with prolonged cardiopulmonary bypass, or in extreme degrees of plasma dilution with a resultant marked decrease of coagulation factors and of platelets.

Summary

Water retention in the body compartments was studied in patients who underwent cardiopulmonary bypass with absolute hemodilution and blood replacement exclusively with nonhemic solutions.

During operation 3½ volumes of fluid had to be administered for each volume of blood lost in order to maintain cardiovascular stability Of this amount, 1 volume was excreted as urine and insensible water loss, 2½ volumes were held in the body ½ volume of it in the blood stream The extravascular to intravascular partition ratio of retained water varied from 1 3 to 1 9

These figures are higher than those usually cited for compartmental equilibration of retained fluid following resuscitative therapy for hemorrhage. It is suggested that water distribution in patients subjected to open-heart surgery is influenced to an appreciable extent by ill-defined effects on the circulation by the mechanics of the bypass procedure itself

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Experimental and laboratory reports

Simulation of atrial flutter by rapid coronary sinus pacing

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The mechanism of atrial flutter remains controversial. Adherents of both circus movement theory and ectopic focus theory maintain the correctness of their views.[1-4]

Most workers in this field produced experimental flutter in dogs by either electrical or chemical means.[5-11] Atrial depolarization was then studied with direct or indirect recording techniques, and the presence of circus movement or ectopic focus was deduced. Electrocardiograms, intracavitary atrial electrograms, and esophageal recordings have been evaluated in patients with clinical atrial flutter to support both of the theories.[12,13]

In this study we have produced an arrhythmia resembling atrial flutter in dogs by coronary sinus and left atrial pacing and in man by rapid pacing of the coronary sinus. The choice of the coronary sinus pacing site was the result of close similarities between direction of atrial depolarization in coronary sinus rhythm inferior left atrial rhythm, and clinical atrial flutter as determined electrocardiographically and vectorcardiographically This will be discussed in further detail.

Methods

Animal studies Seven closed-chested dogs were anesthetized using intravenous chloralose The dogs were placed in the supine position w th limbs parallel to the trunk Bipolar pacemaker catheters (4 to 6 Fr) were positioned with fluoroscopic guidance in the midportion of the coronary sinus. The coronary sinus was paced at a frequency of 200 to 400 per minute using a Grass stimulator with isolation unit delivering square wa e impulses of 2.5 msec. in duration. Voltage was adjusted to a level that produced reliable atrial capture The left cervical vagus nerve was isolated and cut. The distal end was stimulated with a laboratory stimulator† producing varying degrees of A V block to better visualize P waves. Twelve-lead electrocardiograms were recorded on a multichannel oscilloscopic photographic recorder‡ at paper speeds of 25 mm. per second In 2 dogs transseptal catheteri

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†A.E.L. stimulator 104 A, Calmar Pa.
‡Electronics for Medicine, White Plains, N. Y

Table I P wave configuration with coronary sinus pacing in 7 dogs

Lead	P wave	No of dogs
I	diphasic	4
	inverted	3
II	inverted	7
III	inverted	7
V_R	upright	7
V	inverted	7
aV_L	upright	5
	inverted	1
	diphasic	1
V	upright	5
	diphasic	1
	isoelectric	1
V	inverted	7

zation was performed with a Brockenbrough catheter through which a bipolar pacing catheter was positioned in the inferior left atrium Left atrial pacing was then accomplished at rates of 200 to 400 per minute

Human studies Five healthy volunteer male subjects were studied after informed consent was obtained Right heart catheterization was performed in the postabsorptive, nonsedated state with the patient in the supine position With local anesthesia a No 7 Fr bipolar luminal pacing catheter was percutaneously introduced into the right antecubital vein and fluoroscopically positioned in the mid portion of the coronary sinus. The catheter was considered properly positioned when inverted P waves were obtained in Lead II upon electrical stimulation and when withdrawal of blood revealed an oxygen saturation below 50 per cent [14] Pacing was accomplished using an R wave coupled pulse generator which delivered square wave impulses of 2 msec. duration The equipment was carefully grounded and the patient closely monitored during the procedure. Milliamperage was adjusted slightly above the threshold so that adequate pacing could be achieved (1 to 3 Ma.) The coronary sinus was paced at rates of 200 to 350 per minute using the paired mode Twelve lead electrocardiograms were recorded on multichannel oscilloscopic photographic recorders.

Medtronics No 5839 Minneapolis Minn.

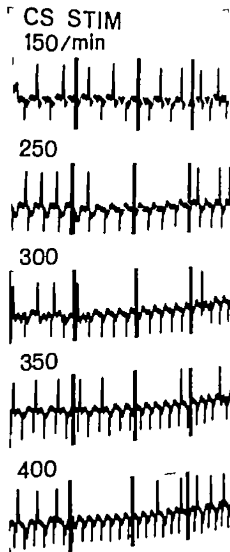


Fig 1 Electrocardiogram in Lead II in a dog Coronary sinus pacing at rates of 150, 250, 300, 350, and 400 per minute. At pacing rate of 150 per minute the appearance is that of an atrial tachycardia. At faster rates the tracing resembles atrial flutter with a sawtooth configuration.

Results

Animal studies Coronary sinus pacing was easily achieved at rates of 150 to 400 per minute The P wave configurations are shown in Table I From an analysis of the P wave configuration in the 12 lead electrocardiogram atrial depolarization appeared to be directed superiorly anteriorly

Electronics for Medicine White Plains N Y Model 4560, New York, N Y

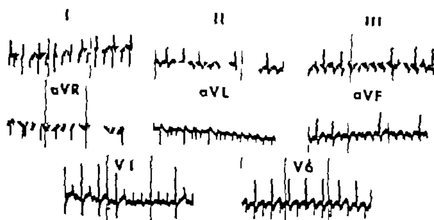


Fig 2. T eh -lead electrocardiogram in dog with coronary inus pacing at 300 per minute. Note typical appearance of atrial flutter. The flutter w es are inverted in Lead II III V V nd V

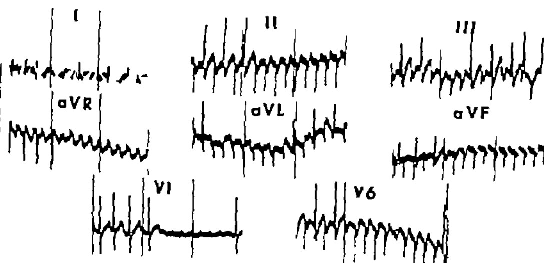


Fig 3. Twelve-lead electrocardiogram in dog with inferior left trial pacing t 300 per m nute. The typical appearance of trial flutter is most marked in Leads II and V Note flutter wa e inversion in II III and V There is also a resemblance to Fig 2.

and to the right. Discrete P waves were noted at rates of 200 to 250 per minute with a clearly isoelectric base line. At more rapid rates (275 to 400 per minute) the P waves became less discrete and an undulating quality with a saw-tooth effect was noted (Fig 1). This was most marked in Leads II III and aV F. In most dogs 1:1 AV conduction was noted up to rates of 330 per minute. In order to better display the F waves at this fast rate A V block was produced by means of vagal stimulation. A representative example is shown in Fig 2. The simulated atrial flutter produced by coronary sinus pacing was not self perpetuating and immediately ceased upon discontinuing pacing.

Pacing from the inferior left atrium produced identical findings to those of coronary sinus pacing. This is illustrated n F g 3.

Human. Pacing the coronary sinus in man produced an arrhythmia similar to those in canines. The P wave was always inverted in Leads II III aV and V_6, upright in aV_R and d phasic or upright in V_1. Varying degrees of base-line undulation were noted at pacing rates above

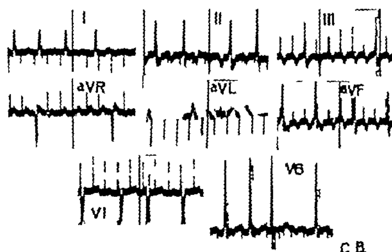


Fig. 4. Twelve-lead electrocardiogram recorded in Patient C. B. during coronary sinus pacing at rate of 3 per minute. Note typical appearance of atrial flutter. Flutter waves are inverted in Leads II, III, aV and

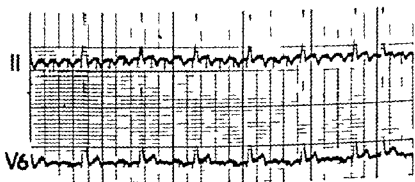


Fig. 5. Simultaneous electrocardiogram Leads II and V during rapid coronary sinus pacing at 300 per m in Patient F. C. Note typical flutter appearance and inversion of flutter waves in these leads.

250 per minute and an arrhythmia resembling atrial flutter was produced (Figs. 4 and 5). Complete atrial capture could not be achieved at pacing rates above 325 per minute. Coronary sinus pacing at rates above 250 per minute usually produced 2:1 or greater degrees of A-V block, thereby allowing good visualization of the F waves. Two patients developed short episodes of atrial fibrillation lasting less than 3 minutes as a consequence of rapid coronary sinus pacing. This occurrence may have been secondary to stimulating in the vulnerable period of the atria.[11] Both cases spontaneously reverted to normal sinus rhythm. No other untoward events were noted. Stimulating the coronary sinus at the milliamperage used in this study (i.e., one to one and one-half times the threshold) never resulted in ventricular pacing.

The electrocardiographic criteria for the diagnosis of atrial flutter are: (1) an atrial rate of 250 to 350 per minute; (2) continuous regular atrial activity with flutter waves identical in spacing, size and contour; (3) continuous undulation of the base line, most often noticeable in Leads II, III and aVF; (4) varying degrees of A-V block.[8]

In the present study the arrhythmia produced in both canines and man chiefly resembled atrial flutter.

Discussion

Several methods have been used for the experimental production of atrial flutter in canines. Lewis and associates

were able to produce short runs of flutter in some dogs following both weak faradic stimulation of the atria at 2 400 to 3 000 stimuli per minute and rhythmic stimulation at rates between 250 to 500 per minute. Rosenblueth and Garcia Ramos[8] more reliably achieved experimental atrial flutter by first interrupting the muscular bridge between the inferior and superior vena cavae and then utilizing electrical stimulation. Scherf also produced atrial flutter in dogs by topically applying acetylcholine,[17] delphinine,[1] and aconitine.[7,8] Prinzmetal and associates used several methods in their studies, but favored the use of aconitine.

Scherf and Cohen[9] producing flutter chemically have been advocates for ectopic stimulation. Prinzmetal and associates, utilizing mostly aconitine induced flutter have shown by both electrocardiographic and cinematographic techniques that there is an ectopic focus in his flutter preparations, with radial propagation of rapid flutter waves from the point of stimulation. They were also able to show that the undulating base line was due to atrial depolarization and repolarization at rapid rates and not due to circus movement. Our study supports the observation that base-line undulation is an artifact of rapid pacing Fig 1 shows that increasing atrial pacing rate above 300 per minute produced a moving base line with a saw tooth configuration.

The evidence for circus movement has been extensively reviewed by Rytand Advocates of the circus movement theory have mostly utilized electrical methods for flutter production. Demonstration of circus movement has been obtained in canines with flutter produced in this manner[14,19,20] Hayden and associates[21] have demonstrated that aconitine flutter is unifocal, while flutter produced by Rosenblueth's technique is circus in character They further suggest that aconitine flutter is not the counterpart of clinical atrial flutter while circus movement is.

Katz and Pick[13] in a discussion of the above controversy have stated that both theories may be correct for different cases of flutter Studies of Lanari, Kato[22,23] and Kishon[23] and their associates support the existence of two types of flutter in man In one type atrial activation appears to be circus-like depolarization of atrial muscle occurring at all times and proceeding in a clockwise or counterclockwise path around the atria In the other type atrial depolarization appears to progress from an ectopic focus with depolarization proceeding cephalad in direction.

Assuming that an ectopic focus is responsible for some cases of flutter the problem then arises as to where the ectopic focus might be located Scherf and Cohen[9] conclude that flutter may arise from the region of the A V node Puech[24] noted that most cases of atrial flutter and A V nodal tachycardias have identical P wave configurations and thus he suggests that flutter may arise from the A V node. Prinzmetal from his study of experimental and clinical flutter believes that the ectopic focus is located caudally in the atria All of the above workers noted flutter wave inversions in Leads II III and aVF suggesting that atrial depolarization was superiorly directed

Mirowski and Alkan[25] have published data showing inversion of P waves in V6 in clinical cases of atrial flutter and suggests that these are variants of left atrial rhythm with atrial depolarization proceeding from left to right Kishon and Smith[23] on the basis of intra atrial and esophageal electrograms postulate that some cases of flutter arise in the low left atrium Hoffman and Cranefield[26] have pointed out that there are automatic cells in the wall of the left atrium at the junction with the pulmonary veins. It is possible that some atrial flutter may arise from these cells.

Pacing of both the coronary sinus and the inferior left atrium produces a P vector that is directed superiorly anteriorly and somewhat rightwards.[14,27] The P wave vector of patients with flutter is directed in a similar fashion (see Fig 6)[28] In addition inversion of P waves in V with coronary sinus rhythm was noted frequently by Spodick and Colman[29] and seen in all the canines and most patients that we have studied[27] Recent work in our laboratory with induced coronary sinus rhythm suggests that atrial depolarization in this condition is directed counterclockwise around the atria with left atrial depolarization preceding right.[30] It thus appears

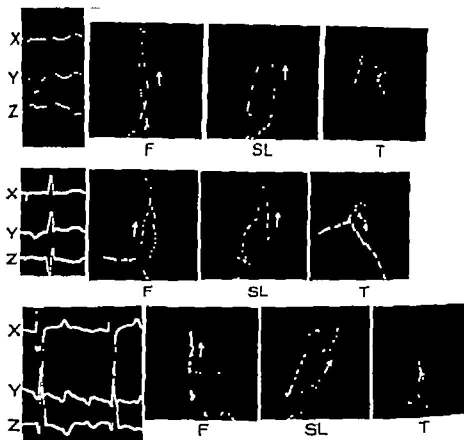


Fig 6 Isolated P vector loops (Frank orthogonal system) with sensitivity of 0 05 mv per centimeter dash time interval of 2.5 msec. *Top* P loop produced by pacing of inferior left atrium of dog *Middle* P loop produced by pacing mid portion of coronary sinus in dog *Bottom* P loop recorded from patient with type atrial flutter Note close similarity in direction and appearance of the P loop in all panels.

that coronary sinus rhythm can mimic "circus movement," in regard to atrial conduction pathways utilized It is intriguing to speculate that perhaps recordings felt to support circus movement are really due to ectopic stimulation with the specialized atrial conduction tissue determining the pathway of atrial depolarization The coronary sinus can produce counterclockwise depolarization of the atria and James has described specialized tracts in the atria which potentially might permit clockwise depolarization from this area.

The coronary sinus has been shown to be an area with a potential for pacemaker activity. Some workers have implied a relationship between the coronary sinus and flutter Giraud and associates precipitated a short run of atrial flutter by probing the coronary sinus in a patient with a known history of paroxysmal atrial flutter This paroxysm ceased when probing was stopped Scherf produced a type of flutter in a dog by mechanically [illegible] ing the coronary sinus with a probe. Zik[illegible] produced an atrial tachycardia with a rate of 330 per minute by warming the coronary sinus in a dog

The similarity in P wave vectors of paced coronary sinus rhythm and clinical atrial flutter coupled with the presence of specific conduction fibers around the coronary sinus, has suggested that the coronary sinus may be a site of origin of some cases of atrial flutter We were able to [illegible] atrial flutter by pacing from the coronary sinus. An identical arrhythmia was produced by pacing the inferior left atrium in canines.

Thus by rapid pacing of the coronary sinus we have produced a [illegible] tachycardia that resembles atrial flutter. Some cases of clinical flutter may [illegible]

focal in origin and thus focus may be in the coronary sinus or low left atrium. The technique described is a safe means of simulating atrial flutter in man and may be of value in helping to better understand this arrhythmia.

Summary

In 5 human subjects and 7 canines, the coronary sinus was paced at rates of 250 to 350 per minute using an electrode catheter. Two of the dogs were similarly paced from the inferior left atrium. An arrhythmia was produced with the following electrocardiographic characteristics: (1) continuous atrial activity with P waves identical in spacing, size, and contour; (2) a suggestion of base line undulation, often with a sawtooth configuration in Leads II, III, and aV_F; (3) varying degrees of A-V block. The arrhythmia produced was not self-perpetuating and immediately ceased upon discontinuing pacing.

The P wave vector of this rhythm was directed superiorly, somewhat rightward, and anteriorly. This is similar to the P vectors of most cases of spontaneous clinical flutter and also to those of both paced and spontaneous coronary sinus rhythms, and inferior left atrial rhythms.

Thus, by rapid pacing of the coronary sinus, and the inferior left atrium, a unifocal atrial tachycardia was produced that resembles atrial flutter. Some cases of clinical atrial flutter may originate as a unifocal tachycardia originating from the coronary sinus or left atrium.

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Fore-'n-aft triangle formula for rapid estimation of area

Dye dilution curve

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The estimation of area inscribed by a dye dilution curve most commonly employs the exponential extrapolation method devised by Hamilton and coworkers.[1] Those employing this method will appreciate the tasks of replotting concentration values on semilogarithmic paper and the integration of these concentration values per unit time. This calculated area is then used in the formula

$$\frac{I \times 60}{A \times cal.f} = \text{Flow}$$

where I stands for the amount of indicator injected, 60 the conversion of second-flow to minute-flow, and *cal f* the calibration factor converting recorder deflection to concentration of indicator.

The above steps render hand calculation of a single emergency cardiac output impractical and that of sequential determinations, impossible. Computer technology has alleviated much of the difficulty by on-line application. However, those of us not so financially endowed have resorted to shorthand methods. The application of the short formulas devised by Dow,[2] Wood,[3] and Hetzel, based on the forward triangle of the dye curve have not been completely satisfactory for the calculation of area (A), especially in low perfusion states. We therefore wish to present a formula of our own design which correlates very well with the standard Hamilton longhand method ($r = 0.998$). A minimum of measurable ingredients and simplicity of mathematical computation make this empirically derived "fore-'n-aft" triangle method even more attractive.

Material and origin of the formula

One hundred dye dilution curves, selected only on the basis of smoothness of contour, were used in comparing the standard Hamilton extrapolation technique with short formulas for estimating area beneath the curves. Subjects consisted of humans, dogs, and rabbits. Indocyanine green dye (Cardio-Green)* was the indicator. Instrumentation consisted of dichromatic densitometers (Waters XC 302, XE 302)† appropriately placed and multichannel recorders (Waters MR 105,† San

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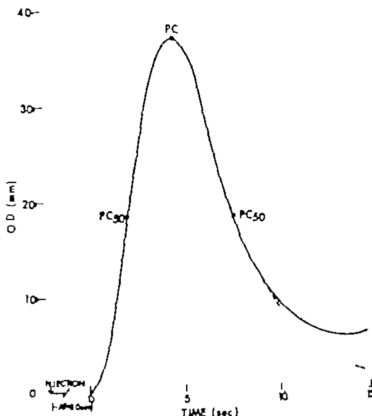


Fig 1 A replot of an actual dye dilution curve is shown with logarithmic extrapolation (broken line) Peak concentration (*PC*) and one half the peak concentration (*PC_{50}*) are identified

born 964 and Beckman RB Dynograph†) The preparation and sudden bolus injection of indicator was accomplished using calibrated syringes (Instrument Associates‡)

The estimation of area beneath a dye dilution curve by inserting an appropriate triangle appeared possible. To account for possible variations in the forward part of the curve relative to concentrations after the peak and to minimize the number of measurements and simplify the mathematics we used the entire area for triangular fit. We applied the geometric principles that a 90 degree triangle has a dimension equal to one half its base at one half its height and that the triangles resulting from diagonal bisection of a rectangle are congruent

In Fig 1 a replot of an actual dye curve is shown The peak concentration (*PC*) and one half the peak concentration (*PC_{50}*) on both ascent and descent are identified

In Fig 2 lines are drawn from PC perpendicular to the time axis and from PC through PC_{50} on the ascent and descent The intercepts are labeled T_{pc} a and d respectively Additional lines are drawn from each PC_{50} perpendicular to the base line and the intercepts labeled T and T respectively Lines are drawn from T and T_d to bisect line PC T_{pc} Thus fore and aft triangle (*a T_{pc}PC*) and (*d T_{pc}PC*) each contain four congruent triangles. The area of a triangle is equal to one half its height times its base The base of each of the four triangles in the fore group is equal to the time span from T to T and henceforth designated T_{a-pc} The base of each of the four triangles in the aft group is equal to the time span from T_d to T_{pc} and henceforth designated T_{d-pc} The height of PC is common to all eight triangles The area of the entire triangular insert (a PC d) within the dilution curve is the sum of (a T_{pc}PC) and (d T_{pc}PC)

*Sanborn Division Hewlett Packard, Waltham, Mass.
†Beckman Instruments Division, Fullerton, Calif
‡Instrument Associates, Northridge Calif

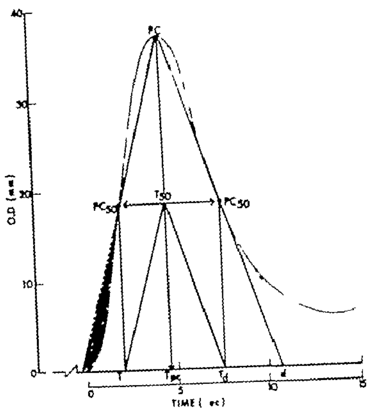


Fig. 2. T sets of congruent triangles are formed within the dye curve of Fig. 1 see text. Note that point may precede the actual appearance of dye. Overestimate of curv area is show by the hash-marked area, the underestimate by the stippled areas.

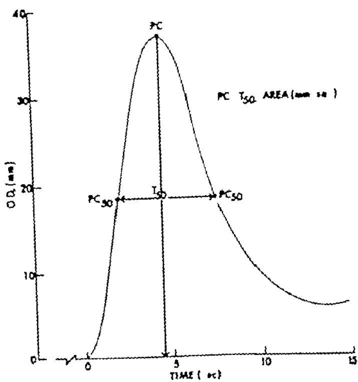


Fig. 3. Only two lines of measurement are necessary for use of the presented formula: peak concentration (PC) in millimeters and the time span (T_{50}) in seconds from PC_{50} on the ascent to PC_{50} on the descent of the curve.

$$T\ PC = 4 \times \tfrac{1}{2}(T_{asc} \times PC_{50})$$
$$T\ PC = 2\,(T_{asc} \times PC_{50})$$
$$T\ PC = T_{asc} \times PC$$

Applying the same steps to $(d\,T_{des} PC)$ the area of the aft triangle becomes $T_{desc} \times PC$. Combining the two major triangles for the total area

$$(T_{asc} \times PC) + (T_{desc} \times PC) = a\ PC\ A$$
$$PC\,(T_{asc} + T_{desc}) = a\ PC\ A$$
$$PC \times \text{total } T_{50} = a\ PC\ A$$

Therefore the time in seconds from PC_{50} on the ascent to PC_{50} on the descent is multiplied by the peak concentration in millimeters to give the entire triangular area beneath the curve expressed in millimeter seconds (mm.-sec.). Fig. 3 shows the actual dye curve with the required measurements for application of this fore-n-aft triangle formula.

Results

The one hundred dye dilution curves were calculated for their individual areas (A) using the standard Hamilton extrapolation technique. Short formula areas were correlated with the Hamilton method as reference. The following short formulas were used:

$$\text{Area} = \frac{C \times t_p}{1 - 0.9\, t_p/t_a} \qquad \text{Dow formula} \quad (2)$$

$$\text{Area} = \frac{2.7}{2.0}\, C\,(t - t) \qquad \text{Wood formula} \quad (3)$$

$$\text{Area} = \frac{C}{k}\,(t_p - t) \qquad \text{Hetzel formula} \quad (4)$$

where C stands for peak concentration, t_p, time of peak concentration, t_a, appearance time, and k constant of 0.37 for central injections of indicator.

Since the Wood and Hetzel formula are essentially the same, varying primarily in constants employed, we report the correlation using $C_p\ (t_p\text{-}t_a)$. In order to substantiate the disadvantage of using only the forward triangle in deriving total area, we also performed a statistical correlation between the forward portion of our formula ($PC \times T_{asc}$) and the Hamilton method. The correlations and standard errors are shown in Table I. Also tabulated are the results using the fore-n-aft triangle formula of our own design, $PC \times T_{50}$.

All three formulas, Dow, Wood, and Hetzel, require corrections of time values for catheter deadspace and several mathematical steps before the final calculation of area is obtained. Benchimol and associates[3] suggest one must be very precise in the measurements of these time segments for accuracy of area determination. Perhaps the difficulty in labeling the precise onset of the dye curve, especially in low perfusion states, contributes to inaccuracies in determining appearance time and build-up time. Use of the "fore-n-aft" triangle formula, $Area = PC \times T_{50}$, gave exceedingly good correlation with the Hamilton method. Fig. 4 is a regression plot of the one hundred dye curve areas. Four values in the high range exceeded three standard errors and we felt justified in considering these as random sampling errors, especially since the majority of curves are below

Table I. Statistical correlations of formulas

	Hamilton	Dow	Wood and Hetzel	$PC \times T_{asc}$	$PC \times T_{50}$
Mean	478.3	341.4	208.5	123.6	[illegible]6.7
S.D.	504.2	495.6	511.6	491.8	431.4
$A_x = a + bA$					
a		124.9	63.6	19.0	−1.94
b		0.564	0.303	0.219	0.84
r		0.754	0.840	0.923	0.9[illegible]
S.E.E.		±206.0	±95.5	±44.2	27

Shown are the mean values and standard deviations (S.D.) for areas (mm.-sec.) calculated by the Hamilton method and short formulas. PC, Peak concentration in mm.; T_{asc}, time in seconds from 50 per cent PC on the ascent to time of PC. T_{50}, time in seconds from 50 per cent PC on the ascent to 50 per cent PC on the descent of the dye curve. A, area by the Hamilton method in mm.-sec. Ax, area by short formulas; r, correlation coefficient; S.E.E., standard error of the estimate in mm.-sec.

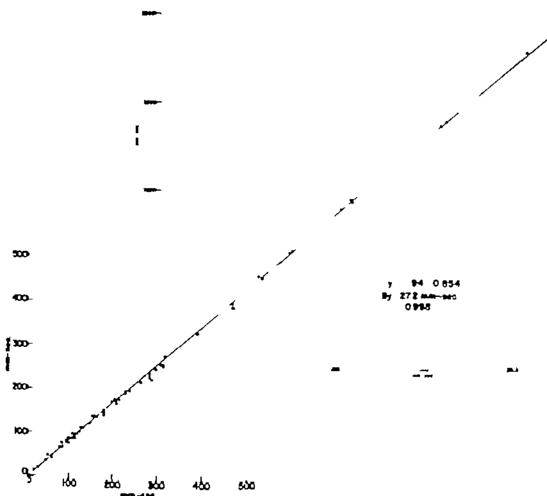


Fig. 4 Areas calculated by the Hamilton extrapolation method, X axis, are correlated with areas derived by the "fore-n-aft" formula, Y axis. An insert magnification of the scale appears at the lower left corner

1,300 mm.-sec. in area. We therefore performed another regression analysis using the remaining curves. The correlation became 0.999 and the standard error of the estimate was reduced almost 60 per cent (± 27.2 to ± 12.5) and the slope was altered very little (Y = −2.3 + 0.856X). All correlation points were now within three standard errors providing a confidence of 99.7 per cent that an estimate by this new formula would be within ± 37.5 mm.-sec. of this mean regression correlation with the standard Hamilton method.

Using the slope of the regression analysis and discarding the small value of the intercept this "fore-n-aft" formula for area can be incorporated into the formula for flow

$$Flow = \frac{I \times 60}{Area_{mm\text{-}sec} \times cal.f}$$

$$= \frac{I \times 60 \times 0.856}{Area(PC \cdot T_{in}) \times cal.f}$$

$$= \frac{I \times 51.4}{PC \times T_{in} \times cal.f}$$

Conclusion

We have presented a simple, rapid, and reliable means of estimating the area beneath dye dilution curves. We have correlated the values obtained with this new formula and those values for the same areas derived by the standard longhand

logarithmic extrapolation method There is an exceedingly good correlation This pertains over a wide range of areas and the values at the extremes probably are areas seldom seen in the clinical setting Since we are using a portable hemodynamic and metabolic monitoring unit for bedside diagnosis and therapeutic guidance in the care of the critically ill patient the pursuit of this investigation had very practical rewards for us in that the formula enables us to give accurate estimates of cardiac output and therefore related parameters and enables us to arrive at these answers very quickly We also recognize the application of this formula in clinical as well as animal research We propose the advantages of the fore- n aft triangle formula to be the following (1) a minimal number of measurements, PC and T_{14} (2) no correction for time which can augment error (3) points of measure fall on the more resolute portions of the curve i.e. no equivocation about time of onset of the curve (4) simplicity of com putation (5) use of the entire dye curve area and thereby avoid the question of relationship of forward and aft triangles and (6) facility for directly incorporating the formula for area into the formula for flow

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Aortic flow velocity in man during cardiac arrhythmias measured with the Doppler catheter-flowmeter system

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Several investigators[1-4] have succeeded in obtaining phasic arterial flow measurements in dogs using sensing devices mounted in the tip of a cardiac catheter. These approaches utilizing the electromagnetic catheter-tip flowmeter[1] and catheter-mounted thermistor flow sensor[4] have demonstrated the feasibility of obtaining such measurements from unexposed blood vessels of animals.

In previous reports, we described our experience with the use of a Doppler ultrasonic flowmeter developed by Franklin[-12] in the study of peripheral arterial flow velocity in man during cardiac arrhythmias[13] and the abnormalities of the flow wave form associated with various types of heart disease.[14,15] Others have also described the usefulness of this approach to study arterial flow distribution.[6-1]

Stegall and associates recently described a Doppler flowmeter-catheter system used to record aortic flow velocity in dogs. It is the purpose of this paper to (1) describe the usefulness of this technique to study aortic flow velocity in man, (2) to describe the normal pattern of aortic flow velocity and its alterations in patients with a variety of cardiac arrhythmias.

Material and methods

Thirty-three patients with spontaneous or induced cardiac arrhythmias were studied. Ten were normal subjects and the remaining 23 had various types of heart disease. In the diseased group, 10 had aortic valve disease, 5 combined mitral and aortic valve disease, 3 congenital heart disease, 2 mitral stenosis and insufficiency, 2 idiopathic complete heart block, and one, an aortic valve prosthesis. Cardiac arrhythmias were detected from Lead II of the electrocardiogram which was recorded simultaneously with the flow velocity curves.

Normal subjects were asymptomatic; their cardiovascular functions were normal as defined by right and left heart pressures determined during catheterization, indicator-dilution measurement of cardiac out-

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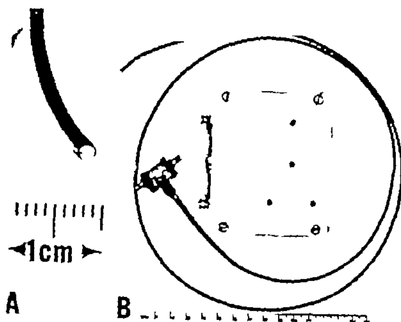


Fig 1 A Enlargement of the tip of No 8 Doppler flowmeter-catheter *B* Doppler flowmeter and catheter

put and selective cineangiography These patients were studied in the cardiac catheterization laboratory because of the presence of systolic murmurs previously diagnosed as representing organic heart disease but in retrospect they were classified as functional murmurs All 33 patients had the anatomic and physiologic diagnosis made on the basis of right and left heart catheterization selective cineangiography and indicator dilution curves.

Instantaneous aortic flow velocity Lead II of the electrocardiogram the phonocardiogram and intracardiac pressures were recorded simultaneously The intracardiac pressures were obtained with saline filled No. 7 or 8 end lumen catheters connected to a P23Db Statham strain gauge

The number of cases with arrhythmias included 30 ventricular extrasystoles, 21 atrial extrasystoles 9 ventricular tachycardias 8 with right atrial and ventricular pacing 5 with atrial fibrillation 2 with complete heart block and 2 with nodal rhythm One or more types of arrhythmias were often present in the same patient In most instances, except for those with complete heart block and those with atrial fibrillation the arrhythmias were of temporary nature and occurred during manipulation of catheters in the cardiac chambers. Cardiac pacing was performed with a Zucker No 8 bipolar catheter placed in the right atrium or right ventricle and connected to the output of a Cordis Synchrocor II pacemaker

Aortic flow velocity was obtained with a Doppler catheter (supplied by Southwest Research Institute) as developed by Stegall and associates, and has been previously described The two hemidiscs of piezoelectric crystals (lead zirconate titanate) oscillating at 8 megahertz were used. The hemidiscs measured approximately 1.5 mm in diameter and were mounted at the end of a standard No. 7 or 8 cardiac catheter (Fig 1) The connections were made to each surface of the discs by No 40 copper wire and these lead wires were soldered to two miniature shielded cables. The catheter tip was finally coated with epoxy (Scotchcast No. 5 3M Company St. Paul Minn.) The catheter was connected to a Doppler ultrasonic flowmeter telemetry system by means of ... The flowmeter telemetry system was built in our laboratory according to Franklin's specifications.[7, 11]

The technique is based on the Doppler shift principle A high frequency sound (7 to 10 megahertz) from one crystal hemidisc is coupled to blood passing through the vascular lumen around the catheter. Part of the emitted sound is backscattered

by erythrocytes and detected by the other crystal hemidisc both are mounted on the tip of the catheter (Fig 1) The reflected signal differs in frequency from the incident signal by a quantity which is proportional to the velocity of the target i.e., red blood cells. Thus, the frequency shift of the backscattered sound is proportional to blood velocity For convenience, *this audio frequency is transmitted via telemetry*

The flowmeter signal is received by a modified Scott FM tuner and amplifier (Model 344) through a standard FM dipole antenna. The demodulated signal is in the audio range and is fed through the tape-out jack simultaneously to a Frazier speaker system for audibly monitoring the flow signals during catheter placement and a Krohn-Hite band pass filter (Model 310C) The filtered output from the latter is fed to a Vidar frequency to-voltage converter (Model 320) where the signal is converted to a DC voltage proportional to the frequency of the received signal An additional filter is necessary at the output of the Vidar unit to smooth out the DC wave form on the Electronics for Medicine oscillograph a resistor of 35 kilo-ohms across two microfarad capacitors accomplishes this final filtering The output is also recorded on magnetic tape. The record is calibrated by taking a known frequency from a signal generator (Hewlett Packard Model 601A) and applying it to the input of the Vidar frequency-to-voltage converter The velocity of blood flow is computed by the Doppler shift formula $\Delta f = \frac{2 f V \cos X}{c}$ where Δf stands for frequency shift f transmitted frequency V velocity of blood X the angle between the sound beams and the axis of the blood vessel and c velocity of ultrasound in the medium In this case sound velocity is equivalent to 1.5×10^5 cm. per second.

Zero flow velocity was obtained by briefly disconnecting the input signal to the frequency meter since zero frequency shift corresponds to zero velocity

The catheter was inserted into the brachial artery after the vessel had been surgically exposed in the right antecubital fossa Under fluoroscopic control the catheter was advanced to the ascending aorta where measurements were made. The tip of the catheter was located at approximately 4 to 6 cm above the aortic valve near the aortic arch Attempts were made to avoid the contact of the catheter tip with the aortic walls or placement near the aortic valves in order to avoid Doppler *shifted reflected sound from aortic wall* or valve motion When this occurred the catheter tip was repositioned in the area of the aortic arch until a clean signal could be obtained The flowmeter audio signal was continuously monitored by means of a speaker and recorded on tape. In addition the analogue record of the flow velocity signal intracardiac pressures, and electrocardiogram were recorded on a multichannel Sanborn tape recorder (Model 3900) and on a DR 12 Electronics for Medicine light-beam oscillographic recorder at various paper speeds

Results

Normal pattern of aortic flow velocity curves The aortic flow velocity curve in man as recorded with this technique consists of a major high frequency systolic wave related to ventricular systole. The onset of this wave follows the QRS complex of the electrocardiogram by about 0.05 second the upstroke of this systolic wave form is normally sharp and rapid (Fig 2) and its peak either coincides with the ascending limb of the T wave of Lead II of the electrocardiogram or precedes it by a short interval. The peak flow velocity in normal subjects and with normal sinus rhythm has a short, sharp peak frequency shift in the range of 3 000 to 8 000 cycles per second (3 to 8 kilohertz [KHz.]) and is followed by a rapid downward slope which terminates at or near base line. This downslope is interrupted by a sharp notch which occurs at the time of the second heart sound of the phonocardiogram and nearly coincides in time with the dicrotic notch of the aortic pressure curve. It appears to represent the end of mechanical systole. The primary wave represents forward aortic flow velocity (i.e., peripherally directed) A secondary wave follows the primary wave, the peak amplitude of which is approximately one third

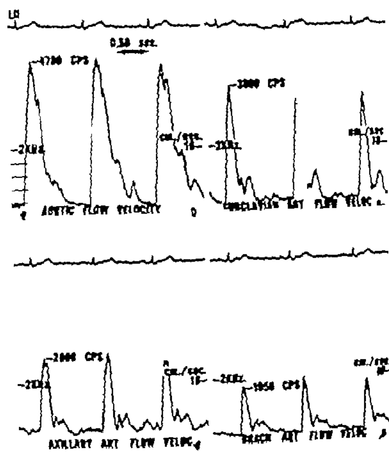


Fig Aortic subcla an artery axillary and brachial artery flow velocity curves recorded with Lead II of the lectrocardiogr m in a 23-year-old man without heart disease. The figures for the peak flow velocity for each curv re ndic ted in cycles per second (cps) on the left side and in calculated velocity on the right. Note progressive decrease in peak flow elocity as the catheter t p is withdra n from the ascending aorta to the right brachial artery The contour of the flow elocity wave form in these various segment of the arterial circulation is essentially the same.

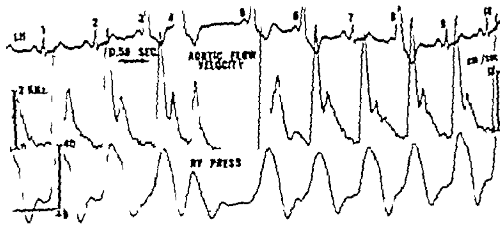


Fig 3 Lead II of the electrocardiogram aortic flow locity and right entricular pressure in patient D H a 62-year-old man ith coronary artery disease. Several extrasystoles occur during the recording. Beat 3 occurs at about the same cycle length during regular si us rhythm (Beats 1 and 2) and it is preceded by a P wave. Note that peak flow locity is identical in Beats 1 and 2. Beat 4 follow Beat 3 by short interval and peak flow velocity decreases significantly Beat 5 is preceded by a long pause and peak flow elocity is increased

of the primary wave. The origin of this secondary wave is not known. It is likely that it represents retrograde flow (i.e. centrally directed) but one cannot be certain of this because this flowmeter unit is not directional. The secondary wave ends in middiastole and the record approaches base line or zero flow.

In general, the normal wave form of the aortic flow velocity curve had the same configuration of the wave form recorded from probes placed around the femoral artery.[20-23] The major differences noted are a higher peak flow velocity, an earlier rise, and a conspicuous secondary wave in the aortic flow velocity curves.

Arrhythmias

EXTRASYSTOLES. Supraventricular or ventricular extrasystoles are associated with peak aortic flow velocity which is directly proportional to the timing of the extrasystole, i.e., the shorter the interval between the extrasystole and the preceding beat, the lower the peak flow velocity (Fig. 3). The minimum length of time for an extrasystolic beat to result in measurable flow velocity appears to be about 0.35 second.

In about 60 per cent of the cases, the peak aortic flow velocity of the postextrasystolic beat was higher than the normally conducted pre-extrasystolic beat and in the remaining 40 per cent of cases it did not change appreciably. This increase in postextrasystolic peak flow velocity was independent of the site of origin of the extrasystole although it occurred more often in patients with ventricular extrasystoles. Moreover, the lower the peak flow velocity associated with an extrasystolic beat, the higher the peak velocity associated with the subsequent beat.

ATRIAL TACHYCARDIA. Runs of atrial tachycardia lasting from 15 seconds to 5 minutes were recorded in 7 patients during which the heart rate ranged from 120 to 250 per minute. With the onset of tachycardia, the peak flow velocity decreased from 20 to 40 per cent of control values.

In 9 patients with pacemaker induced atrial tachycardia, the peak aortic flow velocity remained unchanged until rates of 120 to 140 per minute had been reached beyond which the peak flow velocity decreased by 20 to 60 per cent. This decrease was directly proportional to the heart rate.

Periods of Wenckebach type rhythm with varying degree of A-V block occurred in all cases at pacing rates above 140 per minute. When block occurred irregular flow velocity patterns were always seen. During heart block, the peak flow velocity after a long pause was always greater than the peak flow velocity of beats having the same cycle length as sinus rhythm.

The decrease in peak flow velocity at rapid heart rates was accompanied by a decrease in left ventricular systolic pressure, aortic or peripheral arterial pressure, and by an increase in right atrial pressure.

ATRIAL FIBRILLATION. In atrial fibrillation, peak aortic flow velocity and the area under the curve varied from beat to beat (Fig. 4). These variations were directly proportional to preceding cycle length and inversely proportional to the peak flow velocity of the preceding beat (Fig. 4). Arterial pulse pressure varied with peak aortic flow velocity. These variations were most pronounced when the ventricular rate was above 120 to 140 per minute.

VENTRICULAR TACHYCARDIA. Temporary episodes of ventricular tachycardia were recorded in 9 cases. The heart rates during these episodes varied from 130 to 200 per minute. With the onset of tachycardia, peak flow velocity decreased moderately (Figs. 4 and 5). If the tachycardia persisted more than a few minutes, the peak flow velocity rose slightly, but remained well below the control figures. The most striking finding during this arrhythmia was the irregularity of the flow velocity pattern. Variations in beat-to-beat peak flow velocity were often as high as 80 per cent. Pulsus alternans in the arterial pressure curves occurred in the majority of cases whose rates during this arrhythmia were above 150 per minute. This was also accompanied by "alternans" in the flow velocity curves.

With the onset of pacemaker induced ventricular tachycardia, there was no significant change in peak flow velocity until rates of 100 to 120 per minute had been reached, beyond which there was a precipitous fall in flow velocity by about 60 to 80 per cent of the control levels. The flow velocity pattern at rates above 180 per minute was markedly irregular.

For any given rate of ventricular pacing the peak aortic flow velocity was approxi-

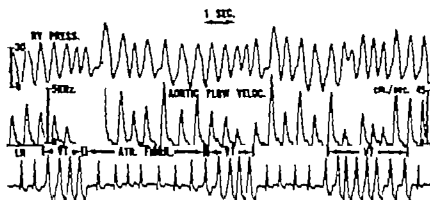


Fig 4 Right ventricular pressure (*RV Press*), aortic flow velocity and Lead II of the electrocardiogram patient N G 43-year-old man with coronary artery disease. The basic rhythm is atrial fibrillation with short runs of ventricular tachycardia (*VT*). Note marked irregularity of aortic flow velocity during atrial fibrillation and reduction of peak flow during ventricular tachycardia.

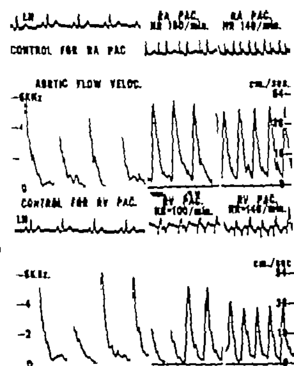


Fig 5 Lead II of the electrocardiogram and aortic flow velocity at rest and during atrial and ventricular pacing in Patient E. T 46-year-old man with a normal heart and functional murmur Note more uniform and higher peak flow velocity during atrial pacing as compared with ventricular

mately 10 to 20 per cent lower than that associated with atrial pacing (Fig 5)

COMPLETE HEART BLOCK Beat to beat variations in peak flow velocity were common in complete heart block (Fig 6) The peak flow velocity and the area under the curves were greater when the P wave appeared 10 to 200 msec before the QRS complex of the electrocardiogram. Within this range of P R interval the peak flow velocity was 10 to 15 per cent greater than beats in which atrial contraction occurred more than 200 msec. before or during the inscription of the QRS complex

Discussion

Measurements of phasic aortic flow during cardiac arrhythmias have not been possible in man because of lack of available techniques. Most of the hemodynamic studies dealing with cardiac arrhythmias have been restricted to measurements of mean flow and to intracardiac and arterial pressures.[29] However recently miniaturization of probes for the electromagnetic and for the Doppler ultrasonic flowmeters allowed the use of these techniques to study central and peripheral circulation in dogs and man

Measurement of blood flow via electromagnetic flowmeters has been obtained in man probes being implanted around the surgically exposed aorta preceding cardiac surgery[31] or on surgically exposed peripheral arteries.[32] More recently there has been a renewed interest in developing techniques for measurement of aortic flow by placing sensing devices at the tip of a cardiac catheter The importance of obtaining such measurements is readily apparent Studies performed in dogs by Pieper,[13] Kolin and associates, and

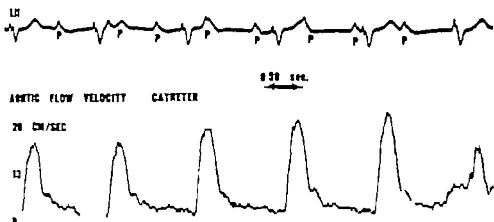


Fig. 6 Aortic flow velocity and Lead II of the electrocardiogram in Patient R. A., 54-year-old woman with complete heart block. The time of inscription of the P wave is indicated. Note progressive increase in aortic peak flow velocity which correlates with P-R interval. The fourth and fifth beats have P-R interval which approaches the normal range. These beats are associated with higher peak flow velocity. The sixth beat has long P-R interval and peak flow velocity is small.

have shown that when a sensing probe is placed at the tip of cardiac catheters and connected to the electromagnetic flowmeter phasic aortic flow velocity can be recorded. Stegall and associates have also shown the feasibility of using the Doppler ultrasonic flowmeter for such measurements in dogs when the crystals are mounted on the tip of a cardiac catheter and connected to the flowmeter.

This report indicates the feasibility of obtaining measurements of phasic aortic flow velocity in man with Doppler catheter-flowmeter system. It is apparent that this technique would be valuable in examining the hemodynamic consequences of transitory cardiac arrhythmias in conscious man.

The arrhythmias described in this report had a variety of origins. The focus of origin (ventricular or supraventricular) did not appear to influence the flow velocity pattern significantly with the exception of ventricular tachycardia which was often associated with marked reduction in aortic flow velocity.

In the absence of appreciable changes in the status of the peripheral resistance the principal determinants of aortic velocity are the stroke volume and the rate of ejection. An extrasystole which begins before diastolic filling is complete would eject a smaller amount of blood and peak aortic velocity would be lower as a result since the postextrasystolic beat usually follows a somewhat prolonged diastolic interval, stroke volume is larger and peak aortic velocity is higher. The importance of timing is shown in Fig. 3: if the extrasystole (either supraventricular or ventricular) begins late in diastole, aortic velocity is relatively normal and little postextrasystolic potentiation is seen. In contrast, very early premature beats generate no measurable aortic flow and were always followed by a beat demonstrating appreciable potentiation.

The same mechanism may be responsible for the reduction in peak flow velocity seen during atrial and ventricular tachycardia, particularly when the rate exceeds 130 to 140 per minute. The shorter diastolic interval allows less time for ventricular filling; end-diastolic and end-systolic volumes fall and stroke volume is reduced. Atrial pacing in chronically instrumented dogs indicates that ventricular volumes are reduced with an increasing rate.[23]

In patients with sinus rhythm, an extrasystole occurring after a diastolic interval of 0.35 second or less caused no measurable flow velocity. However during supraventricular and ventricular tachycardia similar cycle lengths were capable of producing measurable (though reduced) flow velocities. The difference in the effect of cycle length in these two states is likely due to muscular potentiation of some form.[24] During atrial pacing when atrio-

ventricular block occurred the diastolic interval suddenly increased and a higher peak velocity was observed This peak was even larger than that seen at the same ventricular rate during 1 1 conduction suggesting that the preceding period of ventricular tachycardia had somehow potentiated more complete or more rapid emptying

During atrial fibrillation similar cycle lengths were at times associated with different aortic velocities. In particular peak velocity tended to be higher when the preceding beat had produced a relatively low peak velocity This suggests that inadequate ejection leaves a relatively large stroke volume and develops a higher peak velocity The flow alternans seen in patients with ventricular tachycardia might similarly be explained on the basis of alternating increases and decreases in ventricular volume The slight increase in aortic velocity seen in complete heart block when a P wave appeared 10 to 200 msec before the QRS suggests that an effective atrial contraction can increase ventricular and stroke volume by a small though appreciable amount during this rhythm (Fig 6)

Limitations of the technique The most common problem encountered in use of the catheter tip Doppler flowmeter was positioning the catheter tip Placement too near the highly reflected aortic valves or rubbing of the tip along the aortic wall introduced large low frequency Doppler shift signals which could completely obscure the lower level signals from moving blood For this reason the ascending portion of the thoracic aorta is generally unsuitable Our experience suggests that catheters now available should be positioned just below the origin of the innominate artery for measurements in the ascending aorta.

Marked changes in the contour of the flow velocity curve were noted as the catheter was positioned in different locations in the ascending aorta Poor signals were recorded in patients with aortic valvular disease (stenosis or insufficiency) due to either turbulence or a more pronounced motion of the catheter tip during ventricular systole

Recently catheter tip sensors whose source-sensor pairs were angled to one another in order to reduce the distance the sensor sees have been constructed and placement in the aortic root 1 to 2 cm above the valves appears possible They are more sensitive to positioning within the stream however and must be evaluated further to assess their usefulness

The technique offers measurements of blood velocity without the necessity for calibrating each sensor (since they are calibrated by the Doppler shift equation instead) but it does not measure volume flow rate Measurement of the cross-sectional area of the vessel through which velocity is measured would be required to compute for example stroke volume

Some uncertainty about the angle of the tip to the stream renders calibration difficult in areas where the vessel turns sharply as in the aortic arch, but this is a minor problem in relatively straight segments. However the catheter may sample only a portion of the stream and the measured velocity may not be typical of the whole vessel Techniques for positioning the catheter in the center of the stream would reduce this source of uncertainty

The basic Doppler unit available to us does not distinguish between forward (peripherally directed) and reverse (retrograde) flow velocity but inscribes both as an upright deflection on the record McLeod's[15] recent modification of the technique appears to offer some hope of directionally determining flow velocity with the catheter tip device but it has not been widely available and is more complex than the basic instrument.

Advantages of the technique No practical limit on the size of catheter tip Doppler sensors has been found as yet devices as small as 1 mm in diameter have been constructed and others as small as 0 5 mm appear feasible Since the sensors are so small they are easily combined with catheter tip manometers for simultaneous determination of velocity and pressure

Since the blood cell velocity is determined some distance from the tip disturbance of the stream by the catheter's presence should be minimal Moreover angling the sensors to the catheter axis should allow determination of flow velocity in branches of the aorta[16] some ...

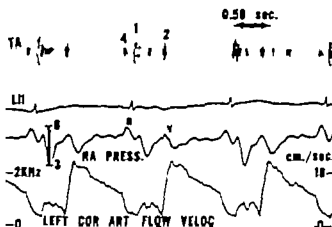


Fig. 7 Phonocardiogram at the tricuspid area (*TA*), Lead II of the electrocardiogram, right atrium (*RA*) pressure, and left coronary artery flow velocity in Patient C. D., a 42 year-old man with chest wall pain and normal selective coronary arteriogram. Note that peak coronary artery flow velocity occurs in early diastole.

efforts in this direction have suggested that coronary flow velocity might be determined by placing a catheter tip Doppler flowmeter near a coronary ostium (Fig. 7).

An additional application for catheter tip Doppler sensors is suggested by the recent report of Maroon and associates[16] who observed with a transcutaneous Doppler ultrasonic sensor that venous air embolism could be detected quickly and easily by listening to the signals generated by reflection from air-blood interfaces. Since certain operative procedures (particularly neurosurgical procedures performed on seated patients) are associated with appreciable hazards from accidental introduction of air into the right heart, a catheter placed in the superior cava could be used to detect these air emboli. In a similar application catheter tip devices have been used to detect circulating gas bubbles during decompression sickness.[17]

As with the electromagnetic catheter tip sensor continuous determination of blood flow velocity with a high frequency response is possible with this approach. General anesthesia and vessel exposure are not required and complications other than those associated with routine catheter placement have not been encountered. Vessels not amenable to transcutaneous examination can be explored and multiple

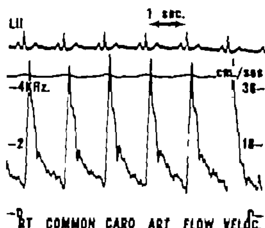


Fig. 8 Lead II of the electrocardiogram and carotid artery flow velocity in Patient E. T., a 47 year-old man with chest wall pain. Note the presence of high diastolic flow in this vessel.

records at various levels in the aorta or other large vessels can be obtained easily (Fig. 8).

In conclusion this technique appears to be of value in the study of hemodynamic consequences of cardiac arrhythmias which are often transitory and difficult to evaluate with previously described approaches. It can also be used to evaluate cardiovascular functions under a variety of conditions,

its major advantages being instantaneous measurement of phasic aortic flow velocity on a continuous basis and the exploration of the arterial and venous conduits of conscious man.

Summary and conclusions

The influence of cardiac arrhythmias on aortic flow velocity using a Doppler catheter flowmeter system was described in 33 patients. The arrhythmias examined included atrial fibrillation spontaneous and pacemaker induced atrial and ventricular tachycardias atrial and ventricular extrasystoles and complete heart block.

Atrial and ventricular tachycardia resulted in a reduced peak aortic flow velocity at rates above 140 per minute. Ventricular tachycardia was associated with marked irregularity in flow velocity pattern with decrease in peak flow velocity for individual beats. Variation in beat-to-beat flow velocity was seen in patients with atrial fibrillation and in patients with ventricular tachycardia this was more pronounced at rapid heart rates.

Factors which regulate stroke volume i e ventricular volume and the influence of previous contractions were discussed in the light of observations made.

It is suggested that this device may be used with caution to study instantaneous phasic aortic flow velocity in conscious man. These observations indicate its potential value in the study of cardiovascular hemodynamics in health and disease.

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Effects of glucagon on myocardial contractility and hemodynamics in acute experimental myocardial infarction

Basis for its possible use in cardiogenic shock

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Derangements of myocardial contractility and peripheral vascular resistance play a major causative role in the genesis of the circulatory failure which may accompany an acute myocardial infarction. Accordingly, augmentation of contractility of the noninfarcted portion of the left ventricle and correction of the altered peripheral vascular resistance constitute two of the major therapeutic aims.

Several investigations reviewed elsewhere[1] have described the use of sympathomimetic amines in the treatment of cardiogenic shock. In a recent report from this laboratory, use of a combination of norepinephrine and phentolamine titrated to elicit an appropriate hemodynamic response was recommended.[1] The use of catecholamines has, however, been criticized on the premise that an outpouring of endogenous catecholamines accompanies acute myocardial infarction.[2] Search for a noncatecholamine stimulant of the heart is therefore warranted.

Interest has recently been focused on glucagon—the hormone secreted by the α cells of the pancreas. First shown by Farah and Tuttle[3] and then by Regan and associates[4] to have positive inotropic and chronotropic action on the heart, an elaborate examination of the mechanism of its cardiac action has recently been reported by Glick and associates[5] and by Lucches[6] These investigators have shown that the cardiac stimulant effects of glucagon were not abolished by blockade of the β-adrenergic receptors in the heart by propranolol. Reserpine-induced catecholamine depletion of the myocardium also failed to dimin the positive inotropic action of glucago These studies suggest that the cardiac action of glucagon is not mediated through the release of endogenous catecholamines. Although the exact biochemical mechan

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through which glucagon acts on the myocardium remains to be identified It has been suggested that its stimulation of the adenyl cyclase enzyme system which catalyzes the reaction resulting in the formation of adenosine 3',5'-monophosphate (cyclic AMP) from ATP may constitute the underlying mechanism[4]

The present investigation was undertaken to evaluate the cardiovascular effects of intravenously administered glucagon after acute experimental myocardial infarction in the dog Its effects on the force-velocity relation of the noninfarcted portions of the left ventricle on mechanical performance of the left ventricle, and on the peripheral vascular resistance were examined

Methods

Experimental studies were performed in 30 mongrel dogs weighing 15 to 22 kilograms and anesthetized with 25 mg per kilogram of pentobarbital given intravenously The trachea was intubated and artificial ventilation, using room air was instituted by means of a Harvard respirator pump Left ventricular and aortic pressures were monitored by means of No. 8 French stiff catheters, directly connected to a Statham P23 DB strain gauge. Zero level for pressure measurements was set at the midchest position. The first derivative of the left ventricular pressure pulse (dp/dt) was obtained by means of an R C differentiating circuit. Left ventricular end-diastolic pressure was recorded using higher sensitivity at the end-expiratory phase of the respiratory cycle. Cardiac outputs were determined from the indicator dilution curves obtained by injecting indocyanine green dye into the right atrium and sampling continuously from the ascending aorta by means of a Harvard withdrawal pump and a Gilford densitometer

An intracardiac strain-gauge catheter assembly described previously in a series of publications[7-9] was used to register curves of fiber shortening Briefly the device consists of two strain-gauge bearing prongs mounted on a flexible stylette which is threaded through an intracardiac catheter With the catheter positioned suitably against the ventricular wall, the prongs are projected from the catheter and engaged into the ventricular wall As the prongs follow the course of fiber shortening in systole, curves of fiber shortening are inscribed on a beat to beat basis. From the simultaneously recorded curves of fiber shortening and pressure pulse instantaneous force velocity relations were determined at an isolength point according to the method described previously The curves of fiber shortening were recorded from the ischemic and nonischemic portions of the left ventricle (Figs. 1 and 2) All events were recorded optically on an Electronics for Medicine recorder Thoracotomy was performed through the left fifth intercostal space and the pericardium was opened anterior to the left phrenic nerve To produce extensive infarction branches of the left anterior descending and left circumflex coronary arteries were ligated. Baseline control measurements were made before the ligation of coronary arteries and were repeated 15 to 20 minutes thereafter Commercially available glucagon (Eli Lilly) was dissolved in the accompanying diluent, forming a solution containing 1 mg per milliliter In 22 dogs, glucagon was administered as a single intravenous bolus injection of 100 to 200 μg Hemodynamic effects were measured in all of the animals myocardial force velocity relation was studied in 15 of them Effects of glucagon were evident in less than a minute the optimum hemodynamic response was observed at 4 to 8 minutes and the effects lasted from 30 to 45 minutes. The readings made at the time of the optimum response were utilized for the statistical analysis using Student's paired t test. In 8 additional dogs, glucagon was administered as an infusion at the rate of 2 to 4 μg per kilogram per minute for a period ranging from 1 to 2 hours, during which time repeated recordings were made.

Calculations of left ventricular minute and stroke work and peripheral vascular resistance were made by conventional methods outlined previously[8]

Results

Myocardial force-velocity relation. Following ligation of the coronary arteries, the ischemic regions of the left ventricle showed rapid decline in the amplitude of systolic fiber shortening followed by a paradoxical

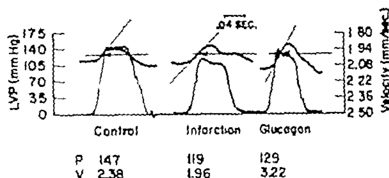


Fig. 1. Effect of glucagon on myocardial force velocity relation in the nonischemic portion of the left ventricle. At an isolength point (indicated by arrows) velocity of shortening (V) was derived by drawing a tangent to the curve of shortening (upper curves), relating height of deflection to time. Scale given with the curve of shortening indicates spacing of the prongs in millimeters. Left ventricular pressure (lower curves) related in time to the isolength point indicated force (P). Glucagon resulted in an increase in the velocity of shortening ($p < 0.001$) and force of contraction ($p > 0.1$) pointing to an augmentation of myocardial contractility. (N of animals = 15)

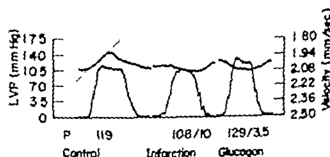


Fig. 2. Effect of glucagon on paradoxic systolic fiber lengthening (upper curves) in the ischemic portion of the left ventricle. After coronary artery occlusion, the curve of fiber shortening (upright curve) is replaced by the curve of fiber lengthening (inverted curve). Glucagon had no appreciable effect on paradoxic movement. (No. of animals = 15)

systolic expansion (Fig. 2). In the nonischemic portions of the left ventricle the pattern of systolic fiber shortening was preserved (Fig. 1). The subsequent administration of glucagon resulted in an increase in the velocity of shortening in the nonischemic portion of the left ventricle ($p < 0.001$) whereas there was no appreciable effect on the amplitude of the paradoxical systolic expansion in the ischemic region (Figs. 1 and 2). The velocity of shortening together with the left ventricular systolic pressure measured at an isolength point before and after glucagon showed that the instantaneous force-velocity relation was shifted upward by glucagon indicating that the drug had resulted in an increase in the contractile state of the nonischemic portion of the left ventricle (Fig. 1).

Left ventricular performance. As shown in Fig. 3 left ventricular function declined after myocardial infarction. There occurred an increase of left ventricular end-diastolic pressure (LVEDP) by 2.8 ± 0.6 mm. Hg whereas left ventricular work per minute fell by 1,979 ± 390 Gm. M. per minute (Table I). Glucagon given subsequently resulted in a fall of LVEDP (4 ± 0.6 mm. Hg) and an increase in left ventricular minute work (2,156 ± 279 Gm. M. per minute) pointing to an augmentation of left ventricular performance (Table I).

As shown in Fig. 4 concurrent with the rise in LVEDP after myocardial infarction there occurred a fall of left ventricular dp/dt (1,496 ± 224 mm. Hg per second) indicative of a decline in left ventricular contractility. Glucagon reversed these changes and resulted in a rise of dp/dt

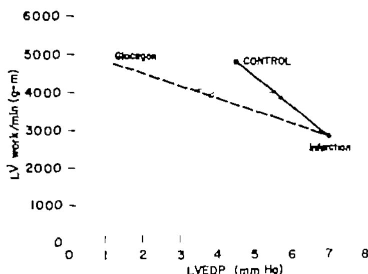


Fig. 3 Effect of glucagon on left ventricular function. Following coronary occlusion, left ventricular end diastolic pressure (*LVEDP*) rose, whereas left ventricular minute work fell. Glucagon reversed these changes by causing fall in LVEDP and an increase in left ventricular work (No. of animals = 22).

Table I Hemodynamic effects of glucagon after acute experimental myocardial infarction (No. of experiments = 22)

			Change from control				Change from infarction		
	Control mean	Infarction mean	Mean ± S.E.	Average (%)	Level of significance (P)	Glucagon mean	Mean ± S.E.	Average (%)	Level of significance (P)
LVSP (mm. Hg)	159	124	−34 ± 5.8	−21 6	<0 001	129	4 ± 2		NS
LVEDP (mm. Hg)	4.2	7	2 8 ± 0.6	66	<0 001	1 87	−4.1 ± 0.68	−58	<0 001
MAP (mm. Hg)	129	104	−24.9 ± 3 8	−22	<0 001	112	10 ± 1.6	9.5	<0.001
dp/dt (mm Hg/sec.)	5 183	3 726	−1 495 9 ± 224	−22.8	<0.001	6,506	2 780 ± 376	75	<0 001
PVR (dynes sec. cm⁻⁵)	5 049	5,207	157 ± 352		NS	3,239	−1 967 ± 249	−37	<0 001
Heart rate (beats/min.)	142	142	−0.1 ± 6		NS	214	73 ± 5.7	51	<0 001
Stroke volume (ml.)	17	12	−5.3 ± 0.9	−30.6	<0.001	14.5	2.6 ± 0.7	22	<0.005
Cardiac output (ml/min.)	2,374	1,624	−749 ± 135	−31.5	<0.001	2,898	1,274 ± 157	78	<0.001
Stroke work (Gm. M.)	32.7	18.3	−14 ± 1.8	−42.8	<0.001	23 4	4.6 ± 1.2	25	<0.005
Cardiac work (Gm. M./min.)	4,843	2,781	−1 979 ± 590	−40.8	<0 001	4 927	2,186 ± 279	76	<0.001

LVSP = Left ventricular peak systolic pressure; LVEDP = left ventricular end-diastolic pressure; MAP = mean arterial; dp/dt = maximum rate of left ventricular pressure rise; PVR = peripheral vascular resistance; SE = standard error; Gm. M. = gram meter.

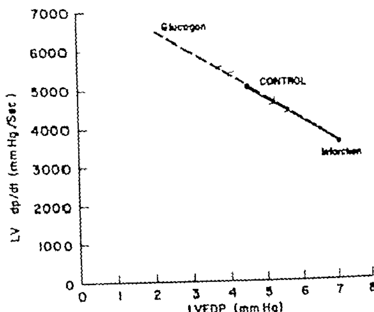


Fig. 4. Effect of glucagon on left ventricular contractility. After myocardial infarction, as LVEDP rose the maximum rate of left ventricular pressure rise (dp/dt) fell. Glucagon, given subsequently, led to a fall in LVEDP and a rise in dp/dt (No. of animals = 22).

(2 780 ± 376 mm Hg per second) as LVEDP fell (Table I).

These changes in left ventricular performance were accompanied by corresponding changes in the ventricular output. Thus after coronary occlusion cardiac output fell by 749 ± 135 ml. per minute; after glucagon cardiac output rose by 1 274 ± 157 ml. per minute (Table I). The stroke volume fell by 5 ± 0.9 ml. per beat after infarction and rose by 2.6 ± 0.7 ml. per beat after glucagon (Table I).

Changes in heart rate varied after coronary occlusion. In 12 of the animals there occurred an increase; a decrease was noted in 9, and no change occurred in one of the experiments. Following glucagon administration heart rate increased uniformly (73 ± 5.7 beats per minute) (Table I). It is evident that the increase in heart rate played an important role in mediating the increase in minute cardiac output as well as the minute left ventricular work observed after glucagon.

Significant changes occurred in the arterial pressure and peripheral vascular resistance (Table I). After coronary occlusion the peak systolic pressure fell by 34 ± 5.8 mm. Hg and the mean arterial pressure fell by 29 ± 4 mm. Hg. The peripheral vascular resistance varied. It rose in 13 of the dogs and fell in the remaining 9. When glucagon was then administered an increase of the peak systolic pressure by 4 ± 2 mm. Hg and of the mean arterial pressure by 10 ± 1.6 mm. Hg was observed. The peripheral vascular resistance fell uniformly in all experiments (1 967 ± 249 dynes cm.$^{-5}$ sec.).

When glucagon was administered as an infusion (2 to 4 μg per kilogram per minute) hemodynamic effects were similar to those observed after a bolus injection. A typical response is shown in Fig. 5. The effect could be maintained throughout the period of infusion which ranged up to ... hours.

A noteworthy feature was a striking absence of cardiac arrhythmias during the administration of glucagon in all of the experiments.

Discussion

It has been reported previously that by employing a strain-gauge catheter assembly it is possible to evaluate the inotropic action of drugs from changes in the instantaneous force-velocity relation of the intact heart.[13] The strain-gauge assembly registers the curves of fiber shorte-

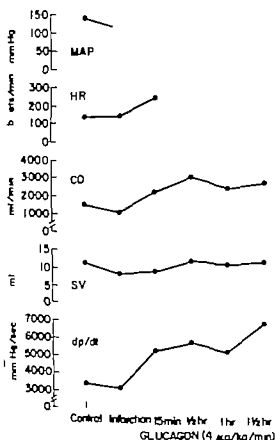


Fig. 5 Hemodynamic effects of an intravenous infusion of glucagon. Except the heart rate, all other parameters fell after myocardial infarction. During glucagon infusion, each showed an increase. *MAP* = Mean arterial pressure; *HR* = heart rate; *CO* = cardiac output; *SV* = stroke volume; *dp/dt* = the maximum rate of left ventricular pressure rise (No. of animals = 8).

ing when its prongs are placed in an axis along which the fibers shorten. If prongs are oriented differently, the tracings obtained are deformed and do not follow the events of cardiac cycle, in which case the prongs are re-inserted until a smooth curve that corresponds to the events of cardiac cycle is obtained. Once properly placed, the position of the prongs is maintained throughout a given experiment. Changes in the inscription of the curve of shortening which may follow an intervention are then attributed to its action in modifying the pattern of fiber shortening.

The present study demonstrates the ability of glucagon to reverse some of the circulatory abnormalities resulting from myocardial infarction. This is accomplished partly by its action in augmenting myocardial contractility of the noninfarcted portion of the left ventricle, as shown by an upward shift in the force-velocity relation [9] observed in this region (Fig. 1). This increase in the velocity of shortening as an index of an increase in myocardial contractile state becomes even more significant, since the left ventricular end-diastolic pressure and hence presumably left ventricular end-diastolic volume fell after glucagon (Table I). Although some of the increase in velocity of shortening resulting from glucagon may be due to an increase in frequency of contraction, it is unlikely that the entire effect of the drug is mediated through this mechanism, since the inotropic effect of the drug has been shown to persist even after the chronotropic effect is blocked. This effect of glucagon is in accord with its positive inotropic action demonstrated in the isolated heart muscle preparation.[6,7]

The effect of glucagon on myocardial contractility is further reflected in the rate of left ventricular pressure rise. The left ventricular dp/dt is principally determined by the ventricular end-diastolic volume and the contractile state of the heart muscle.[10] The fall in left ventricular dp/dt observed after myocardial infarction, despite the rise in LVEDP, indicates a decline in left ventricular contractility (Fig. 4). The subsequent rise in dp/dt concurrent with a fall in LVEDP induced by glucagon points to its effect in augmenting myocardial contractility.

Additional evidence for the cardiotonic effects of glucagon was obtained from the ventricular function curves. It is seen from Fig. 3 that the decline in left ventricular function observed after myocardial infarction was reversed by glucagon, which resulted in an increase in left ventricular work performed from a lowered level of left ventricular end-diastolic pressure. The action of glucagon in augmenting myocardial contractility in cat papillary muscle preparations was shown by Glick and associates[6] and by Lucchesi. In their studies, glucagon resulted in an increase in the maximum developed tension and shifted the force-velocity curve upward and to the right. In the intact dog, glucagon was found

to increase cardiac performance which was not blocked by the prior treatment with propranolol. Further, the inotropic effect of glucagon was reported to be independent of hyperglycemia since the simultaneous administration of insulin to maintain the blood sugar at a constant level did not diminish the positive inotropic response to the drug.

The cardiac output, which had decreased after myocardial infarction, rose after glucagon (Table I). This was mediated through both an increase in stroke volume and an increase in the heart rate. Other investigators have reported an increase in cardiac output resulting from glucagon regardless of an increase in heart rate.[11,12] The marked acceleration of heart rate induced by glucagon in the present study has not been reported in human subjects[11,14] and hence may either be a species-specific response or may be related to anesthesia.

The variable effect of acute coronary occlusion on the pattern of peripheral vascular resistance observed in the present study is similar to that reported in patients with acute myocardial infarction.[2] This has been attributed to the fact that after myocardial infarction, due to the mechanisms as yet not well identified, the reflexes normally activated by a fall in cardiac output may or may not prevail or may be supplanted by other reflexes.[11,4] Glucagon given to animals after coronary occlusion resulted in a uniform decline of systemic resistance. It is not definitely known whether this effect is due to a direct vasodilation or secondary to an increase in cardiac output. Decrease in vascular resistance induced by glucagon was shown to occur in perfused hind limb experiments of Glick and associates;[4] this vasodilation occurred despite β-blockade with propranolol. A modest fall in systemic resistance resulting from glucagon has also been reported in other studies on the intact man and animals.

The action of glucagon resulting in a fall of systemic resistance combined with its effect in maintaining an adequate level of mean arterial pressure and cardiac output is central to its possible use in the treatment of circulatory failure which may accompany acute myocardial infarction. Its effect in augmenting cardiac contractility may also render it suitable in the treatment of myocardial failure. This will, however, depend upon whether glucagon has a favorable effect on the ratio between myocardial oxygen consumption and oxygen supply. The increase in heart rate and the augmentation of myocardial contractility should result in an increase in myocardial oxygen consumption.[17] This may partly be compensated for by the decline in left ventricular afterload resulting from the fall in peripheral vascular resistance. Regan and associates[4] reported an increase in respiratory quotient and oxygen uptake of the heart in dogs after the administration of glucagon. Goldschlager and associates[8] from this laboratory have reported an increase in myocardial blood flow parallel to the increase in myocardial oxygen consumption in man after glucagon. However, a similar relation between myocardial oxygen demand and oxygen supply in the type of experimental preparation employed in the present study remains to be established.

The strongly positive chronotropic effect[18] of the drug is not desirable; however, this effect is less marked in man.[11,18] The characteristic absence of cardiac arrhythmias with glucagon renders it safe for use in myocardial infarction where the threshold for arrhythmias is generally elevated. In this respect, it seems to offer an advantage over isoproterenol since the latter is known to enhance the automaticity of the heart. In several other respects, the action of these two drugs is similar;[11] e.g., both are characterized by a positive inotropic and chronotropic action on the heart and both result in a decline of systemic vascular resistance. Like isoproterenol, glucagon is not likely to be useful in cases with diminished peripheral vascular resistance. Unlike isoproterenol, however, glucagon can be used as an effective cardiac stimulant in the presence of β-adrenergic blockade produced by drugs like propranolol. This is of some importance since propranolol may be employed to counteract cardiac arrhythmias in myocardial infarction. Snow and associates[13] have recently reported that use of propranolol resulted in a significant decline in the mortality rate from acute myocardial infarction. The use of propranolol under these circumstances is, however, marked by the hazard of pre-

tating heart failure.[3] This is likely to be prevented by the simultaneous use of glucagon.

In the ischemic region of the left ventricle resulting from the ligation of coronary arteries, there occurred a rapid decline in the amplitude of fiber shortening followed by a reversal in the direction of inscription of the curve (Fig. 2). Since the position of the prongs of the strain-gauge assembly had remained unchanged, this indicated replacement of systolic fiber shortening by fiber lengthening. These findings are similar to those described first by Tennant and Wiggers[22] who regarded such paradoxic fiber lengthening as a passive distension of the noncontracting ischemic myocardium yielding to the forces generated by the surrounding contracting myocardium. Glucagon was found to have no significant effect on the paradoxic systolic distension (Fig. 2). Since the contractile activity is absent in the ischemic myocardium, glucagon is not likely to exert a direct effect in this region. The lack of an increase in paradoxic movement may be related to the manner in which glucagon alters the kinetics of contraction in the nonischemic regions of the left ventricle.

Summary

Effects of glucagon administered intravenously either as a bolus or as an infusion were investigated in dogs with acute myocardial infarction. Glucagon was found to augment the contractile state of the noninfarcted portion of the left ventricle as indicated by an upward shift of the force-velocity relation.

Left ventricular performance as estimated from the relation between left ventricular end-diastolic pressure and left ventricular minute work fell after myocardial infarction. In a similar manner, the left ventricular contractility as defined by the rate of left ventricular pressure rise from a given level of left ventricular end-diastolic pressure also showed a decline after myocardial infarction. Glucagon reversed these changes. It resulted in a lowering of left ventricular end-diastolic pressure and an increase in left ventricular work and the rate of left ventricular pressure rise. Cardiac output, which fell after infarction, rose after glucagon.

Glucagon resulted in a rise in the mean arterial pressure from the lowered values which prevailed after infarction. The peripheral vascular resistance varied after infarction. After glucagon, there was a uniform decline in peripheral resistance. While an increase in the heart rate as a manifestation of the positive chronotropic effect of glucagon was marked, absence of cardiac arrhythmias was noteworthy.

These effects of glucagon point to its potential therapeutic value in the treatment of the circulatory and/or myocardial failure which may accompany an acute myocardial infarction.

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Alternate deletion and potentiation as the cause of pulsus alternans

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Pulsus alternans is a disorder characterized by alternating strength of the pulse in the absence of arrhythmia or of significant variation in interval between beats. Since Traube's[1] initial description in 1872, the condition has been regarded as a myocardial dysfunction of weak beats alternating with normal beats. Wiggers[2] considered the possibility that one of the pair of beats might be supernormal, but concluded that the condition always involved deletion of contraction of some myocardial fibers alternating with normal contraction of all fibers. Until very recently[3-5] most proposed mechanisms of pulsus alternans have involved heterometric autoregulation (Frank-Starling relationship).[6]

We have developed a method for producing pulsus alternans in healthy intact animals, which permitted us to test the hypothesis that heterometric regulation accounts for alternation in stroke volume. In addition, we have tested for the possibility that aortic back pressure in conjunction with the Frank-Starling relationship might support sustained alternation. Concluding that linear relationships could not explain pulsus alternans, we suggest a new mechanism, that of alternate deletion and potentiation.

Material and methods

A thoracotomy was performed on 15 dogs of random breed under aseptic conditions and under pentobarbital anesthesia. Pulsed ultrasonic flow transducers were implanted on the ascending aorta in every animal and in some instances on the pulmonary artery, the superior vena cava and a pulmonary vein. Bipolar electrodes for stimulation were sewn onto the left atrial appendage. Miniature mutual inductance coils, 8 mm in diameter, consisting of 200 turns of 1 mil enamel-covered wire, were sutured onto opposite sides of the left ventricle at its greatest anterior-posterior diameter. A large diameter

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thick walled Silastic tube was passed di rectly into the left ventricle through the apex and retained by a purse-string suture A small flat Silastic balloon was placed in the pleural space All electrical leads and cannulae were brought out to the dorsal chest wall After complete recovery and never less than five days after the surgery the animals were lightly anesthetized with morphine (2 to 3 mg per kilogram intra muscularly) and pentobarbital (15 mg per kilogram intravenously) Up to four

channels of flow were recorded with pulsed ultrasonic flowmeters.[7] One of the mutual inductance coils was excited by a 100 k current The induced current from the secondary coil was demodulated, amplified, and recorded so that an upward recorder deflection represented an increase in di ameter of the left ventricle Calibration was obtained by use of a modified method[7] and the average variation in diameter was 2.0 mm. for an average in ternal end-systolic diameter of 45 mm. ...

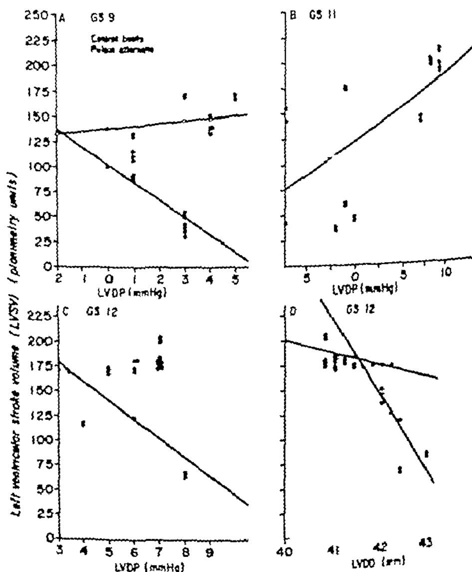


Fig 1 F ur graph relating left entricular trok ol me (LVSV) t left entricular end-d ... (LVDP) and left entricular end-dia tolic diameter (LVDD). Regres ion lines are dra ... beat without lternation nd for teady-state cond tion with pul us alternans at ... such as GS-9 identifies the animal. Note the neg tive slope for 3 of the 4 relationships during ... positive lope for GS-11 is not ignificant for the alternating beats.

these relatively small excursions (less than 5 per cent) the mutual inductance method is essentially linear.[14,31] Pressures were recorded with Sanborn 267B transducers. Arterial pressure was obtained from either the femoral or carotid arteries. In the animals with flow transducers on the main pulmonary artery, right ventricular pressure was obtained by catheterization of the femoral or jugular vein under fluoroscopic control.

After control recordings at fast paper speed (100 mm per second) the animals were paced at the slowest rate that was tolerated without interference from the sinus node pacemaker, usually 90 to 100 beats per minute. Without pause the rate was abruptly doubled and in most experiments, sustained pulsus alternans appeared. If not, the right vagus nerve was exposed in the cervical region and the nerve was stimulated using an Electrodyne stimulator. The atrial pacing was repeated and with few exceptions, pulsus alternans could be produced.

The analogue data were manually reduced to digital form from four of the experiments and in two experiments an on

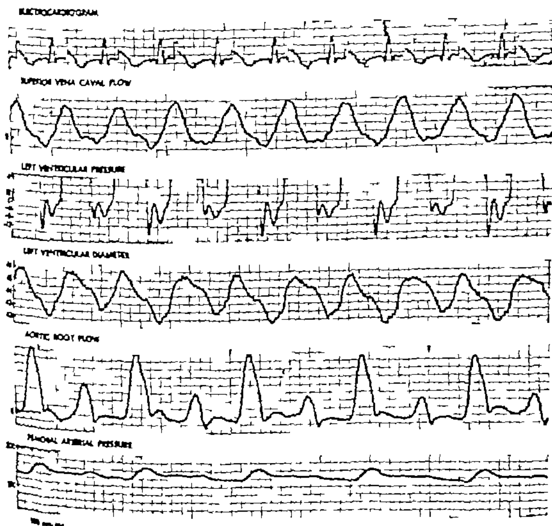


Fig. 2. Rapid atrial pacing in a healthy animal under light anesthesia with morphine and pentobarbital. Note the absence of significant alternation in ventricular diastolic pressure or diameter. This animal is the same as Cy-11 in Fig. 1. Zero flow levels are determined by acetylcholine-induced cardiac arrest.

line analogue-to-digital converter was used and the data were edited and analyzed with a small, high-speed computer (Raytheon 440) In the majority of experiments the manually reduced data were analyzed either on the Raytheon 440 or on an IBM 7090 for descriptive statistics and simple and partial correlation coefficients. A minimum of 25 beats were analyzed from each stable condition.

The animals were terminated and subjected to postmortem examination no significant pathologic changes were found

Results

The correlations of left ventricular end diastolic pressure and diameter with left ventricular stroke volume during pulsus alternans are presented in Table I The correlation coefficients were usually not high and frequently were negative Also plotting the individual stroke volume against either pressure or diameter for non alternating beats and alternating beats revealed a marked separation of the two sets of data from the same animal (Fig 1) not compatible with a single ventricular function curve.

Aortic diastolic pressure had a consistently higher (negative) correlation with left ventricular stroke volume in pulsus alternans than did the filling pressure (Fig 2) The effect of the back pressure on the left ventricular systolic pressure is much less than on stroke volume during alternation shown by lower correlation coefficients and by the markedly smaller variance for systolic pressure (average S D of ± 6 per cent) compared to the stroke volume (average S.D of ± 53 per cent)

The beat by-beat relationship of the input to the output for the right and left ventricles in pulsus alternans was investigated in three animals. There was no alternation of the caval inflow in the presence of right ventricular alternans, and similarly a dissociation between input and output for the left ventricle In fact, there was a *negative* correlation between pulmonary vein flow and the following left ventricular stroke volume This is consistent with our failure to find a significant positive correlation between left ventricular diastolic diameter and stroke volume in pulsus alternans (Table I).

If the ventricular myocardium failed to relax in pulsus alternans as suggested by some,[11,12] an elevation of the early diastolic pressure in the left ventricle should occur following a strong beat and the subsequent beat would be weak. We measured the lowest pressure with each beat in the left ventricle during early diastole (LVDPE) and found a positive correlation between LVDPE and the following left ventricular stroke volume (LVSV) whereas a negative correlation would be expected if failure of relaxation caused the alternation.

Discussion

Although previous reports have indicated that the strength of contraction in pulsus alternans was not predictably related to the ventricular diastolic pressure as the Frank Starling relationship was purported to operate through alternating fiber length However pulsus alternans can be observed

Table I Correlation coefficients for left ventricular stroke volume (LVSV) and (1) left ventricular end-diastolic pressure (LVDP) and (2) aortic diastolic pressure (ADP) and (3) left ventricular end-diastolic diameter (LVDD) of the preceding beat during pulsus alternans

Experimental animal	*No. of beats*	*LVSV vs LVDP*	*LVSV vs ADP*	*LVSV vs LVDD*
GS-1	158	614	− 701	
GS-3	60	364	− 795	− 1L
GS-	25	035		09
GS-9	25	− 485	− 75	C5
GS-11	25	018	− 677	− 41
GS-12	25	− 526	− 814	

in fixed length muscle preparations,[4] and some clinical observations have failed to show alternating end-diastolic volume.[14] Our data showed no consistent correlation between the stroke volume and either end diastolic pressure or diameter (Table I Fig. 1) The Frank Starling school [12] has contended that inadequate myocardial relaxation[13] could occur on an alternating basis and that the length of the contractile element may be alternating even though external dimensions were unchanged due to variation in the series elastic component. If the contractile element failed to relax after a strong beat, the subsequent weak beat would begin with the contractile element in a shortened state and therefore at a disadvantage from the length-developed tension relationship Inadequate relaxation should be most evident in early diastole, at the time when the ventricle pressure is the lowest, presumably due to elastic recoil of the ventricular wall Consequently if inadequate relaxation caused a weak beat, the higher early diastolic pressure (LVDPE) would be associated with a smaller stroke volume (LVSV) in the next beat, and a negative correlation would occur between LVDPE and LVSV We found the opposite, a positive correlation between these variables (Table II) Similarly if the ventricle failed to relax venous inflow should be reduced if the venous pressure and filling interval are unchanged but we found no such relationship between caval flow or pulmonary vein flow in association with alternation of the respective ventricles.

Even if a consistent alternation in end diastolic pressure or volume could be demonstrated it would not establish causality no matter how a strong beat was produced it is reasonable to expect a smaller residual volume after ejection. However the relatively simple Frank Starling relationship would not sustain a complex oscillation such as pulsus alternans. The very term heterometric autoregulation [12] implies a restorative force tending toward equilibrium not the instability of an oscillation

Aortic diastolic pressure the back pressure which must be overcome by the ventricle before there is ejection has been an important variable in most systematic approaches to control of stroke volume in the normal but has been surprisingly neglected in pulsus alternans. Our data show a highly consistent and significant negative correlation for the preceding aortic diastolic pressure and the left ventricula stroke volume (Table I) n contrast to the correlation between ventricular diastolic pressure or diameter and stroke

Table II. Correlation coefficients in the same animal with and without pulsus alternans

Parameters	LVDD	LVDPE	LVDPL	ADP	ASP	LVSV
			Control state			
LVDD	1 000					
LVDPE	— 635	1 000				
LVDPL	— 304	0 471	1 000			
ADP	— 734	0 198	0 178	1 000		
ASP	— 709	0 584	0 520	0 747	1 000	
LVSV	— 651	0 714	0 476	0 405	0 639	1 000
			Pulsus alternans			
LVDD	1 000					
LVDPE	— 373	1 000				
LVDPL	— 830	0 615	1 000			
ADP	— 475	— 003	0 388	1 000		
ASP	— 112	0 463	0 388	— 255	1 000	
LVSV	0 075	0 621	0 048	— 677	0 848	1 000

Abbreviations LVDD Left ventricular diastolic diameter; LVDPE, left ventricular diastolic pressure early LVDPL, left ventricular diastolic pressure, late (presystolic) ADP aortic diastolic pressure ASP aortic systolic pressure LVSV left ventricular stroke volume

volume This relationship between aortic diastolic pressure and stroke volume is predictable a priori with constant heart rate and an unchanged peripheral resistance the aortic back pressure at the onset of a weak beat will be higher than before the onset of a strong beat Considering the disadvantage of overcoming a greater back pressure a smaller stroke volume might be produced even if the ventricular end-diastolic volume and pressure were identical for two successive beats. Thus alternation of aortic diastolic pressure as with the ventricular diastolic volume would tend to exaggerate the effect of alternation on stroke volume but whether these two factors operating in a linear system can sustain pulsus alternans must be examined

Wiggers[3] pointed out that pulsus alternans was frequently provoked by premature ventricular contractions in patients that were predisposed to the condition In our experiments premature ventricular contractions at slower rates would cause alternation in stroke volume for only two or four beats but in animals paced at higher rates, extrasystoles would frequently produce or exaggerate sustained alternation Using a premature ventricular contraction as a transient disturbance with an otherwise constant heart rate and utilizing linear equations ($f(x) = a + bx$) the effects of ventricular filling and aortic diastolic pressure on stroke volume are graphed in Fig 3 A With the premature contraction filling interval is shortened and the end-diastolic volume will be 75 per cent (to allow for end-systolic volume control end-diastolic volume is set at 125 per cent) If the stroke volume for the premature beat is proportional to the preceding diastolic volume relative to the control beat the stroke volume of the extrasystole will be 60 per cent of the control stroke volume The subsequent beat after a compensatory pause will start with a small residual volume but will fill for a greater interval than normal and will have an end-diastolic volume of 165 per cent The proportional stroke volume will be 132 per cent of the control but the subsequent residual volume is reduced to very near the normal Continuing the calculations for each beat the effect of the extrasystole on diastolic volume, and thus stroke volume dies out in only two beats after the extrasystole. In Fig 3 B the linear effect of aortic back pressure is added to the effect of varying ventricular diastolic volume Each stroke volume is calculated first on the basis of end-diastolic volume (stroke volume A) and then adjusted for aortic back pressure (stroke volume B) Although alternation occurs for one pair of beats after the extrasystole it disappears thereafter Thus aortic back pressure is more effective in producing alternation than heterometric autoregulation alone but neither of these linear relationships is capable of producing sustained alternation alone or together. Although the Frank Starling stroke volume/diastolic volume relationship is curvilinear limiting or even descending after an optimal filling volume is reached, adjusting the equations for this by utilizing an exponential would result in even less tendency for instability i.e., the effect of the transient would be less pronounced initially and would die out sooner Similarly if the equation for aortic diastolic pressure were more realistic, reflecting the observed exponential fall rather than a linear fall with time there would be more of a smoothing effect following the transient disturbance

We conclude that heterometric autoregulation cannot account for pulsus alternans for the following reasons. (1) Correlation coefficients between stroke volume and ventricular end-diastolic pressure and diameter were usually not high and were frequently negative (2) No evidence was found of inadequate diastolic relaxation that might obscure a heterometric relationship for the contractile element (3) Using linear equation heterometric autoregulation will *restore* stability after a ventricular premature contraction and not sustain alternation.

Alternate deletion and paradoxical bulging. Alternate deletion of contraction of some myocardial fibers is probably the best established explanation for pulsus alternans in certain pathologic states. Green[11] showed in 1936 that ischemic areas of myocardium not only failed to contract with alternate beats, but sometimes bulged during contraction of the nonischemic areas of r[illegible]

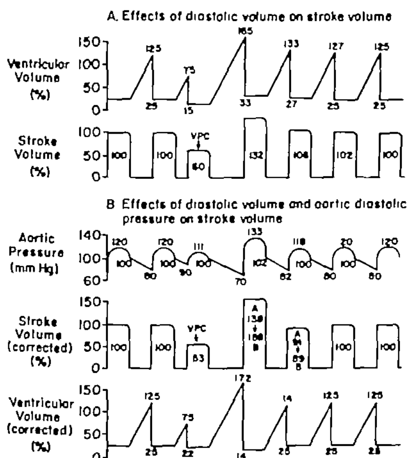


Fig 3. A, Graph of the calculated effect of a entricular premature contraction (VPC) on stroke olume and entricular filling The calculations are based on the following linear equations

$$(1)\ \textit{Ventricular diastolic volume}\ (VDV) = \textit{Residual volume}\ (RV) + \ kt$$

$$(2)\ \textit{Stroke volume}\ (SV) = \frac{VDV}{VDV} \times SV_c$$

$$(3)\ RV = VDV - SV$$

SV represents the control stroke vol me (100 per cent), k constant indicating consta t filling rate, and t for diastolic interval. VDV is the control diastolic olume B Graph of the effects of VPC on stroke olume through an interaction between entricular filling and ortic back pressure, based on the three equations in Section A, further corrected by these four equations

$$(4)\ SV_{corrected} = SV \times \frac{\textit{Aortic diastolic pressure}\ (ADP)}{\textit{Aortic diastolic pressure}\ (ADP)}$$

$$(5)\ \textit{Aortic systolic pressure}\ (ASP) = ADP + \frac{SV}{SV} \times \textit{Pulse pressure}_c$$

$$(6)\ \textit{Early aortic diastolic pressure}\ (EADP) = ASP - \tfrac{1}{2}\ PP$$

$$(7)\ ADP = EADP - ct.$$

ADP represents the preceding diastolic pressure in the aorta, and ADP is the control level, 80 mm. Hg PP represent the control value for pulse pressure 40 mm. Hg The constant indicates constant run-off rate for aortic diastolic pressure. Note that I situation governed by entricular of me alone, no alternation occurs. If the aortic back pressure is added as determinant, alternation occurs for only four beats (starting ith the VPC), before the control relationship is restored.

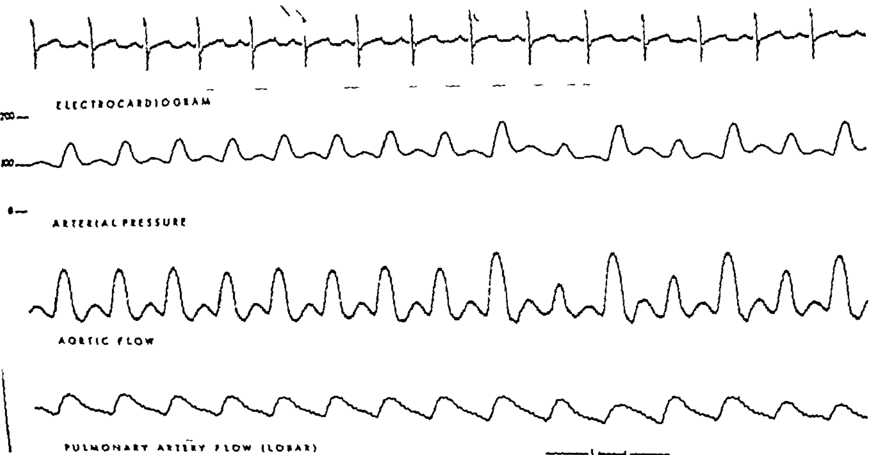
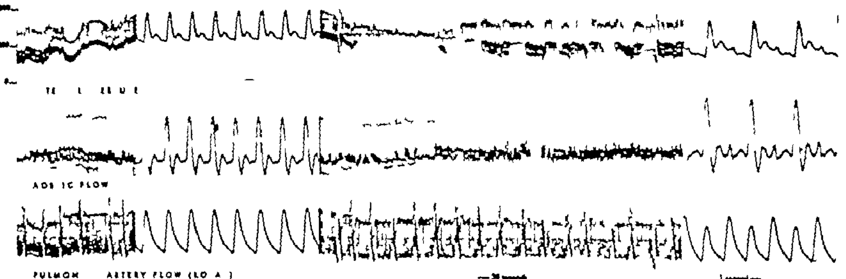


Fig. 4 Spontaneous development of marked pulsus alternans in dog sedated with morphine, apparently initiated by supernormal beat [illegible] pressure and flow pulse in the aorta. (Closer inspection reveals slight alternation [illegible]) Note the absence of regular alternation in the pulmonary artery. Calibration [illegible] flow [illegible] this experiment [illegible] chronic [illegible] Amplification for the lobar pulmonary artery flow [illegible] times that for the descending thoracic aortic flow. Arterial pressure was obtained by needle in the femoral artery. The latter [illegible] large [illegible] increased slightly (40 msec) [illegible] small [illegible]



5 The effects of 40 μg of norepinephrine intra enously on the same dog in Fig 4. Pulsus alternans, which had ppeared spontaneously is abolished momentarily but reappears n the middle of the record. The gradual reappearance of the alternation is seen as progressive decline in aortic pressure and flow of every other beat and an increase in the other half of the beats. The alternation is much less n the pulmonary artery nd the alternans is discorda t between the aorta and pulmonary artery

cardium We accept deletion of contraction of a portion of the myocardium due to failure of electromechanical coupling as a fundamental process of pulsus alternans. In addition we propose that energy made available by the activation process but not used in the noncontracting cells is conserved and appears in the following beat as a potentiated contraction resulting in alternation of weaker than average (for a given heart rate and basal state of contractility) with stronger than average beats. Results from our studies supporting this hypothesis follow

The record that first suggested to us that potentiation was involved in pulsus alternans is shown in Fig 4 The alternation occurred spontaneously in a healthy dog lightly anesthetized with morphine and pentobarbital The first beat with marked alternation (the ninth beat in Fig 4) is stronger than the normal beats and is preceded by a slight increase in cycle length to 500 msec compared to the previous intervals of 460 msec The succeeding weak beat also is preceded by a 500 msec. interval but the aortic flow velocity is less than one half of the strong beat. The total area under the flow curves for the weak and strong beat is approximately the same as the total for two normal beats. The pulmonary lobar flow in this record is characteristic in its independence of the alternation of the left ventricle When alternation was present in the right ventricle it was invariably less marked than in the left and although generally the alternation was concordant for the two ventricles discordant alternation was not uncommon (Fig 5)

The presence of potentiation of the strong beat in pulsus alternans had previously been reported by others.[4,1] In our systematic study of alternation produced by fast atrial pacing accurate comparison of stroke volume with and without alternation was possible Pacing the right atrium at a rate only 3 per cent faster than the spontaneous sinus rhythm produced a 1 per cent increase in stroke volume Doubling the rate produced pulsus alternans however the *mean* of the stroke volume during pulsus alternans actually exceeded one half of the stroke volume when the heart was paced at one half the rapid rate, by a ratio of 1 15 1 Thus, the mean stroke volume and cardiac output did not fall with pulsus alternans in this healthy animal although the rapid rate (over 180) was one at which a decrease in cardiac output has been reported with pulsus alternans.[11,23] Considering that half of the beats produced very little, and some times no forward flow potentiation of the strong beat is necessary to maintain a normal mean

Further evidence that the mean output of the left ventricle in pulsus alternans is conserved by a combination of deletion and potentiation is seen in the latter half of Fig 5 in which a "double staircase" phenomenon is seen with one half of the beats showing a progressive increase and one half a progressive decrease. In this animal spontaneous pulsus alternans was present in the initial 15 seconds of the record and was abolished by norepinephrine intravenously As the effect of the drug wears off the "double staircase" emerges. The double treppe has been reported by others[14] in association with pulsus alternans.

Our data and data of others provide strong evidence of potentiation in at least some instances of pulsus alternans. Potentiation in current use refers to increases in contractility which are the direct result of changes in rate or rhythm[24,25] as contrasted to increases in contractility due to changes in fiber length or afterload to changes in fiber length or afterload Potentiation occurs with increasing rate[26] and with extrasystoles,[27] labelled frequency and prematurity potentiation, respectively[25] Koch Weser and Blinks[25] suggested that potentiation is produced by accumulation of the positive inotropic effects of activation (PIEA) These authors denied that PIEA was "consumed" by contractions, but the data of ... Vaughan Williams[29] and others[30] clearly indicate that the decay of potentiation with paired pulse stimulation and extrasystoles is beat-dependent. On the other hand the potentiation seen with rate increase requires several beats to accumulate in contrast with prematurity potentiation

Potentiation as a result of premature excitation releases sufficient energy to attract clinical interest. With paired p

stimulation, a second stimulus is applied sufficiently close to the first so that only a single effective contraction is observed for the pair. Potentiation, however, is found only if there is a second propagated action potential and an associated contractile event.

A basic fact of prematurity potentiation as seen in paired-pulse stimulation is the difference in the rapidity of recovery of the electrical process in contrast to the mechanical process of the myocardial cells: excitability recovers rapidly and contractility much more slowly.[28] If the recovery

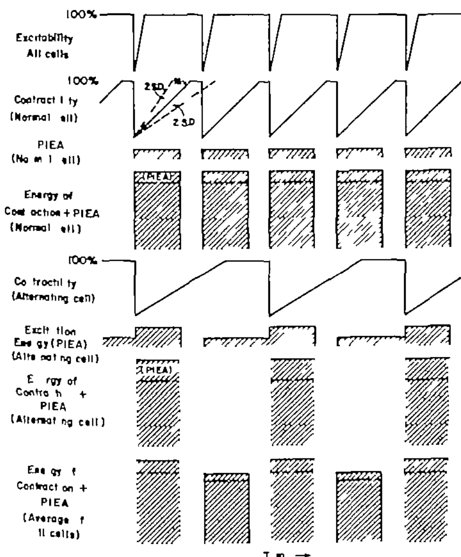


Fig. 6. Graph of relationships based on the proposed hypothesis for pulsus alternans, alternate deletion, and potentiation. The rapid recovery of excitability permits all cells to be depolarized with each cycle. The recovery of contractility is much slower and with short intervals, a varying percentage of the cells have not recovered completely so that this population of cells will be excited but will not contract. The potential energy released by electrical activation (labelled *PIEA*) is not manifest until contraction occurs. In the majority of the cell population, this energy is utilized during each beat, but in the population with slower recovery contraction occurs only every other beat. The energy from the deleted contraction is stored until the next activation, so that the strength of contraction for the alternate beat is greater than average. The net effect for the ventricle, or muscle strip, is alternation of weak and potentiated beats; the exact relationship depends upon the proportion of cells that are alternating.
The use of PIEA here is intended as an abbreviation for a concept suggested by Vaughan-Williams and is somewhat different from the concept of Koch-Weser and Blinks.[illegible] See text.

of contractility is slow relative to the heart rate there is a possibility that a varying population of cells will not contract with the next electrical impulse whether originating in the sinus node or in an external pacing device (Fig 6) In a fraction of the cells deletion of contraction would permit the accumulation of the energy released by activation for *two* beats resulting in potentiation of the second of the pair of beats. Synchronization of the population of cells with slow recovery would assist in the recognition of pulsus alternans ventricular premature contractions provoke alternation in patients that are otherwise liable to pulsus alternans.[1] With synchronization pulsus alternans appears as an alternation between (1) beats generated by part of the cells contracting normally and (2) beats generated by contractions of all the cells, some of which are potentiated (Fig 6) The size of the cell population involved in alternation does not have to be as large as the variance in stroke volume suggests in the Results section we showed that the average variance of the stroke volume was 58 per cent while the average variance of the left ventricular systolic pressure was 6 per cent.

Alternate deletion and potentiation could explain a wide variety of conditions known to be associated with pulsus alternans in man experimental animals, and papillary muscle preparations. Any form of myocardial disorder particularly if accompanied by tachycardia could cause failure of contraction in some cells with alternate beats. Hypothermia would slow all metabolic processes, including restitution of the contractile apparatus.[4,22] Rapid pacing[4,6] may exceed the ability of even the healthy myocardium to restore 100 per cent of the cells to normal contractility in the interval available Vagal stimulation recently shown to have a *moderately* depressing effect (23 per cent reduction) on ventricular contractility [23] was usually effective for us in producing pulsus alternans at rates that did not cause alternation without vagal stimulation It is intriguing that the first laboratory demonstration of pulsus alternans was by Gaskell in 1882 who stimulated the vagus in frogs.[24] Morphine in the doses used in these experiments appears to have a vagotonic effect and alternation was more difficult to produce without morphine.

Finally the usefulness of systems analysis as an approach to periodic functions in pathophysiology seems evident. Milhorn and Guyton[25] in approaching Cheyne-Stokes respiration deduced that the instability involved either an extremely high gain or a long delay (namely a long transport time) or an interaction. Similarly in pulsus alternans, simple relationships such as the Frank-Starling mechanism are unlikely to account for a complex oscillation A delay in the recovery cycle of myocardial contractility could account for fractional deletion of contractile elements and if conservation of energy from electrical activation is added a unifying hypothesis for pulsus alternans is plausible that of alternate deletion and potentiation

Summary

We have tested the hypothesis that pulsus alternans could be explained by heterometric autoregulation Dogs were aseptically prepared one week in advance with ultrasonic flow probes, pressure cannulae dimension transducers (mutual inductance and sonar methods) and atrial stimulation electrodes. Under light morphine-nembutal anesthesia rapid pacing usually produced alternation. The aortic back pressure had a consistently high negative correlation with left ventricular stroke volume (LVSV) The correlations of end-diastolic pressure and diameter with LVSV varied widely and were frequently negative Modeling of the linear effects of ventricular diastolic volume and aortic back pressure on LVSV demonstrated prompt restoration of equilibrium after a transient disturbance rather than a sustained alternation We agree with early theories of alternate deletion of contraction of some myocardial cells but present evidence that potentiation is also inherent in pulsus alternans. All cells recover excitability in the interval available but only a fraction may be restored to normal contractility. This population of cells are then excited but do not contract allowing the energy from excitation to remain available for the next beat which will then have [illegible] the amount of energy of excitation [illegible] the alternate beat will be potentiated

similar to the mechanism of paired pulse stimulation.

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Case reports

Coronary embolism in primary myocardial disease

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The clinical features and complications of primary myocardial disease have been described in several recent reviews.[1-4] Systemic emboli arising from mural thrombi in the ventricles, are known to occur during the course of the disease. Sudden death has also been noted and has been attributed to arrhythmias or pulmonary embolism.[1-4] Coronary embolism has not been reported as a complication of this disease nor as a cause of death The following report presents two patients with primary myocardial disease in whom coronary embolism occurred

Patient 1 G W

This 31-year-old Negro male was admitted with history of dyspne nd pain in the chest. He had been w ll til three week prior t admission when he developed severe precordial pain which was relieved with rest. A few d y later cough nd malaise appeared and persisted in pit of treatment with ntibiotics H became incre ingly short of breath nd had frequent episodes of paroxy mal nocturnal dy pnea associated w th precordial pain.

Three month prior t admission, he had had transient, pal less hematuria. There w no hi tory of rheumatic fever hyperten ion, or alcoholism. N family history of heart disease or hypertension obta ned.

On examination, he was orthopneic and appeare acutely ill. There was sinus tachycardia ... alternans, the venous pressure elevated, ... the blood pressure was 120/90 mm. Hg ... precordial heave extending t the anterior axilla line was noted. Auscultation revealed alternation the intensity of the heart sounds and ... rhythm. No murmurs ere heard. Numerous ... pulmonary ales, an enlarged, tender liver and ... edema were also present. Chest x-ray reve ... eralized cardiomegaly Left atrial and left ... lar hypertrophy ere seen in the electrocard... (ECG) (Fig 1 A). Blood cou t, blood ure ... transaminases, and a sickle cell preparation were normal.

With bed rest, digitalis, and diuretics there ... marked symptomatic improvement The ... pressure fell, and the gallop rhythm disappeared Seven days after admission, he developed sudden ... hemiplegia, follo ed within a few hours by ... Profound hypotension persisted in spite of ... ment, nd de th occurred t day l ter ... taken on the day of death rev aled a left ... I the electrical axis nd S-T segment elevated ... Lead II III V and the right precordial le... (Fig 1 B).

At topsy ther w cardiomegaly the he... weighing 620 gram and showing dilatat n of the chambers. A recent myocardial infarct, the ...

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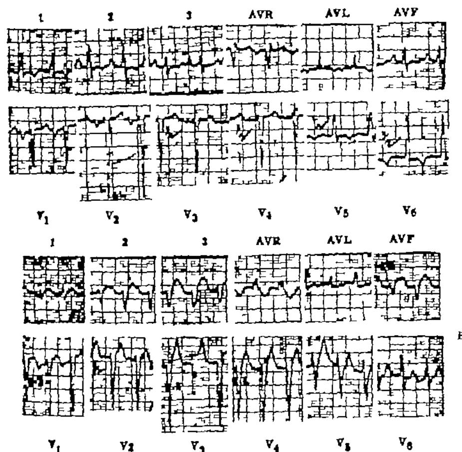


Fig. 1. *A*, ECG of Patient 1, G. W., on admission (Nov. 19, 1964) showing left atrial and left ventricular hypertrophy. *B*, ECG on the day of death (Nov. 28, 1964) reveals a change in the electrical axis and S-T segment elevation in Leads II, III, and aV

of which was estimated to be 48 to 72 hours, was seen in the anterior wall extending into the interventricular septum. There was no evidence of valvular disease. Mural thrombi, not related to the area of infarction, were seen in the cavity of the left ventricle. The coronary arteries were free from atherosclerosis. There was an embolus in the anterior descending branch of the left coronary artery. Smaller branches of the left anterior descending coronary artery also showed occlusion by thrombi. Histologic examination of the coronary arteries did not reveal any evidence of atherosclerosis (Fig. 2, *A*). Embolic occlusion of the right internal carotid artery, with extensive infarction of the right cerebral hemisphere, and multiple, recent, renal infarctions were also seen. Histologic examination of the myocardium disclosed a recent myocardial infarction (Fig. 2, *B*). Noninfarcted areas of the myocardium revealed interstitial myocardial fibrosis. Severe bilateral venous congestion and areas of viral pneumonia were seen in the lungs. Attempts to isolate virus from the myocardium were unsuccessful. There was no histologic evidence of hypertensive vascular disease.

Comment. The absence of coronary artery disease, valvular disease, and hypertensive cardiovascular disease confirmed the clinical diagnosis of primary myocardial disease. During the short course of his illness, this patient sustained cerebral, renal, and coronary embolism. Death resulted from myocardial infarction and cardiogenic shock. In view of the evidence of multiple systemic emboli, it is tempting to attribute the precordial pain at the onset of the illness to a separate episode of coronary embolism.

Patient 2. L. O.

In July, 1960, during a routine examination for urinary infection, this 30-year-old Negro male was noted to have cardiomegaly on x-ray and left ventricular hypertrophy on the ECG. There were no cardiovascular symptoms, and no abnormal physical signs were detected in the cardiovascular system. Four months later he was admitted with left hemiplegia of sudden onset. Examination of the cardiovascular system revealed a regular pulse, blood pressure 140/100 mm. Hg, and normal heart sounds. A diagnosis of hypertensive cardiovascular disease

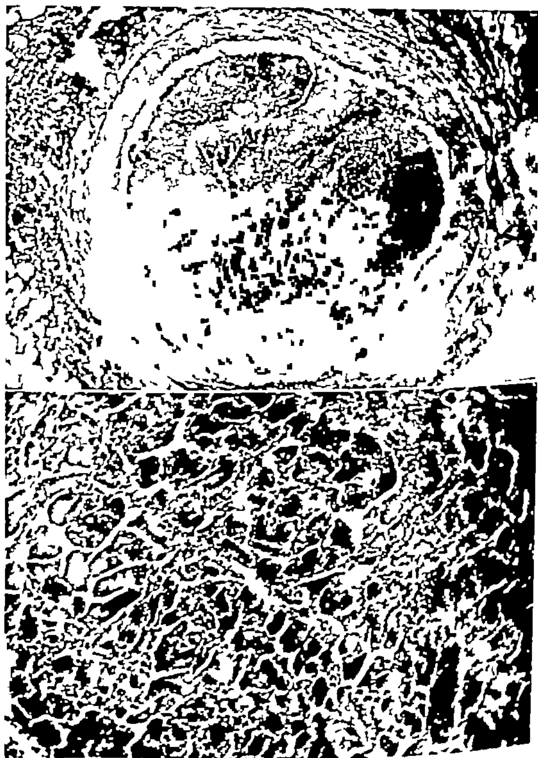


Fig 1 Section show embolus in the coronary artery of Patient 1 Not the normal arterial all B Pl micrograph of the myocardium howing a recent myocardial infarction.

as considered, but subsequent blood pressure recordings were entirely within normal limits. A few days after admission, he complained of severe precordial pain associated with dyspnea. Widespread symmetrical T-wave inversion, compatible with subendocardial infarction, was seen in the ECG (Fig. 3). Precordial pain and dyspnea recurred in short episodes over the next few days but eventually subsided. No further ECG were taken. With partial recovery of power in the left arm and the leg, he was discharged. During the next two years, he was seen on several occasions with the main complaint of pain in the chest. The pain was described on occasions as squeezing and retrosternal but had no consistent relation to exertion. Physical examination revealed no abnormality other than cardiomegaly and blood pressure readings ranged between 110/80 to 130/90 mm Hg. The heart size assessed radiologically was noted to vary from almost normal to definite cardiomegaly. ECG continued to show evidence of left ventricular hypertrophy. There was, in addition, questionable evidence of healed inferior wall infarction (Fig. 4). In March 1963 he was admitted with a history of increasing dyspnea, and examination revealed congestive heart failure with a loud gallop rhythm and

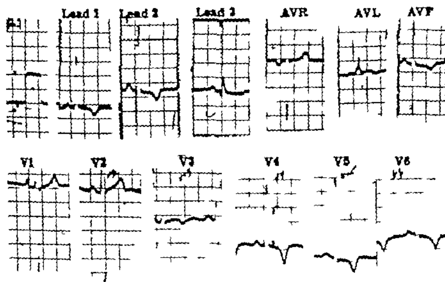


Fig. 3 ECG of Patient 2 immediately following the episode of precordial pain. Widespread, symmetrical T-wave inversion compatible with a subendocardial infarction is seen.

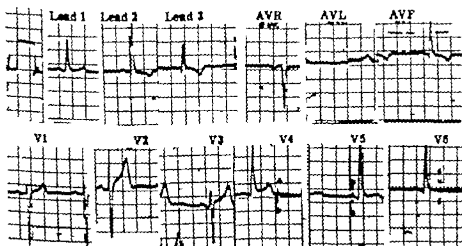


Fig. 4 ECG of Patient 2 t months after the initial episode of precordial pain (see text).

an apical pansystolic murmur. There was minimal left hemiparesis. With bed rest, digitalis, and diuretics, there was marked symptomatic improvement. The apical pansystolic murmur disappeared, but the gallop rhythm persisted. A greatly reduced cardiac output and elevation of the filling pressures in both ventricles were found on cardiac catheterization. There was no stenosis or insufficiency of any of the cardiac valves. Symptomatic improvement continued, and a few weeks after admission, he was discharged. A year later he developed right hemiplegia, and was admitted once again. Anticoagulant therapy was started in the hope of preventing further systemic emboli, but cardiac failure began to get steadily worse and within the next few months he was admitted for the last time with severe congestive heart failure. He died two days after admission. Initial blood pressure recordings during the first two admissions disclosed mild elevation of the diastolic pressure but on both occasions, the blood pressure returned to normal with rest.

At autopsy, the heart weighed 750 grams. There was hypertrophy and dilatation of all the cardiac chambers. The left ventricular wall measured 15 mm. in thickness and the right ventricular wall 4 mm. Large mural thrombi were seen in both ventricles. An extensive healed myocardial infarction, involving the inferior wall and extending to the lateral wall, was seen. The coronary arteries were patent and showed no evidence of atherosclerosis. Histologic examination of the myocardium revealed a healed myocardial infarction, focal interstitial fibrosis, and hypertrophy of some of the myocardial fibers. Numerous healed infarcts of both kidneys, healed infarction of the spleen, and old infarcts in both cerebral hemispheres were also seen. Microscopic examination of the kidneys revealed areas of infarction and focal areas of cellular infiltration compatible with focal pyelonephritis.

Comment. The course of this patient's illness was dominated by embolic episodes. Indeed, at one stage symptoms and signs of cardiac insufficiency were insignificant. Although there was mild elevation of the blood pressure on occasions, the blood pressure returned to normal without antihypertensive therapy. The absence of persistent hypertension and the absence of histologic evidence of hypertensive vascular changes at autopsy exclude hypertension as the cause of cardiac failure in this patient. Coronary embolism most probably took place shortly after the first episode of cerebral embolism when the patient developed severe precordial pain associated with widespread symmetrical T-wave inversion in the electrocardiogram. The failure to demonstrate the embolic occlusion of a coronary artery at autopsy is not surprising in view of the length of time that elapsed between the clinical episode and death and can be explained on the basis of clot fragmentation and lysis.

Discussion

Clinical reviews on coronary embolism have emphasized the rarity of this entity and the part played by bacterial endocarditis in its etiology. Wenger and Bauer[9] in their review proposed rigid criteria for the diagnosis of coronary embolism. These included, in addition to the identification of the source of the embolus, the demonstration of an occluding mass in the lumen of a coronary artery and a normal arterial intima at the site of the occlusion. Patient 1 in this report satisfied all these criteria. In Patient 2, the source of the embolus and normal coronary arteries were demonstrated but an occluding mass was not seen in any of the major coronary arteries. The length of time between the clinical episode and the patient's death probably accounts for the failure to find an embolus in the coronary artery. Recurrent systemic embolism, the clinical episode of sudden precordial pain, and myocardial infarction in the absence of coronary artery disease all point to a diagnosis of coronary embolism.

Although coronary embolism has not been mentioned as a complication in recent reviews on primary myocardial disease,[1] a careful scrutiny of the earlier case reports of primary myocardial disease reveals instances of coronary embolism. Thus, Levy and Rousselot[18] in their paper in 1933 describe an 18-year-old male and a 22-year-old male both of whom had primary myocardial disease and coronary embolism. Hamman,[1] reviewing 40 reported cases of coronary embolism due to various causes, refers to two of his patients with primary myocardial disease who developed coronary embolism. Two additional reports[illegible] describe patients with primary myocardial disease in whom systemic embolism had occurred and autopsy revealed myocardial infarction in the absence of coronary artery disease.

Pain in the chest has been a feature in many reported series of patients with primary myocardial disease.[illegible] While it was vague and nonspecific in many instances, angina has occurred in some. In one large series of patients,[3] angina occurred in 10 out of 216 patients. Precordial pain has been explained as resulting from relative coronary insufficiency due to a low cardiac output or occasionally as a associated pericarditis.[3] Mural thrombi and systemic emboli are common in primary myocardial disease and it is possible that coronary embolism plays a role in the genesis of

angina in at least some of these patients. A similar explanation has been proposed for the occurrence of angina in mitral stenosis.[15] It is also possible that instances of sudden death that have been encountered in primary myocardial disease[1,2,3] may have resulted from coronary embolism It would seem likely that coronary embolism would be more prone to occur in patients with multiple systemic embolism such as the two patients described in this report.

Summary

Two patients in whom coronary embolism occurred in association with primary myocardial disease are presented In addition to coronary embolism multiple systemic embolism occurred in both patients In Patient 1 cerebral embolism preceded coronary embolism by a short period of time, and death resulted from myocardial infarction and cardiogenic shock In Patient 2, the patient survived the episode of coronary embolism but had episodes of precordial pain for some months following coronary embolism and continued to have multiple systemic embol It is suggested that some instances of angina and sudden death in primary myocardial disease may be due to coronary embolism.

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Transvenous cardiac pacemaker, mural thrombosis, and pulmonary embolism

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Treatment of heart block by transvenous catheter pacing is an effective therapy which does not require a major surgical procedure. However complications have been encountered including pacemaker failure because of displacement of the electrode from the right ventricle, power unit failure, wire breakage or loss of contact with a responsive endocardium, wound infection, and perforation of the heart.

Thromboembolic complications have been rare during transvenous pacing and no difference in voltage requirement or thromboembolism has followed anticoagulant prophylaxis.[1-3] Deposition of a black material about an electrode has been reported by Gordon and venous inflammation and thrombosis have been noted.[4,5] Fatal pulmonary embolism followed the development of a right ventricular thrombus in a case described by Goldberger.

We are reporting a case of pacemaker failure with unusual and illuminating features.

Case report

A 76-year-old man developed complete heart block in 1966. A left ventricular transthoracic pacemaker was implanted and he did well until June 1, 1968, when he had an acute episode of weakness and dizziness due to battery failure. On June 6, 1968, a permanent *transvenous* pacemaker was inserted into the right ventricle. He was readmitted on Sept. 21, 1968, because of intermittent episodes of weakness and dizziness during the preceding two weeks. Three days prior to admission, he had noted episodes of paroxysmal nocturnal dyspnea.

Upon admission, response to pacemaker impulses was irregular and ventricular rate varied from 40 to 60 beats per minute. Increasing the amplitude and the rate of stimulation failed to remedy the situation. However, positioning the patient on his left side increased the number of impulses that were effective.

On Sept. 24, 1968, a temporary demand pacemaker was inserted under fluoroscopy. During the insertion of the new pacemaker catheter into the right ventricle, it passed alongside the old pacemaker wires (Fig. 1). At this time, the patient

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Fig. 1. The portion of the second electrode alongside the malfunctioning transvenous catheter is seen. The inactive old transthoracic pacemaker remains implanted in the left ventricle.

suddenly complained of acute left anterior chest pain. The new demand pacemaker was placed on standby. However after the onset of chest pain the patient followed the original pacemaker regularly regardless of position.

The chest pain was pleuritic in character and within 30 minutes a pleural friction rub could be heard over the left lower chest. Chest roentgenogram 1½ hours after the onset of his pain showed blunting of the left costophrenic angle. On Sept. 25, 1968, lung scan was compatible with a left lower lobe pulmonary embolus (Fig. 2). Creatine phosphokinase activity (CPK) was 36 U (normal) serum lactic dehydrogenase (LDH) was 255 U (normal 0 to 200) bilirubin was 0.6 mg per cent. Heparin was administered and the old pacemaker continued to function well. The new temporary demand pacemaker remained on standby

Over the next 48 hours, chest pain subsided and the pleural friction rub disappeared. On Sept. 28, 1968, a large painful hematoma appeared in the right buttocks at the site of an injection given prior to anticoagulation. Due to this, heparin therapy was interrupted on Oct. 1 1968. During the evening of Oct. 2, 1968, several episodes of nonconducted pacemaker impulses occurred. The irregular cardiac response to the pacemaker continued despite ample impulse voltage. Heparin therapy was restarted on Oct. 4 1968, and by the evening of Oct 5, 1968 pacemaker response returned to normal. On Oct. 8 1968, the temporary pacemaker wires were removed. A bit of material attached to the electrode tip proved to be an organizing thrombus upon histologic examination. Coumadin was administered and when prothrombin times were within therapeutic range, heparin was discontinued. The pacemaker has functioned normally since then.

Discussion

Pacemaker failure occurred in this patient despite the fact that the electrode position in the right ventricle was confirmed radiologically. The pacemaker impulse blip was large and rhythm was regular. These observations are consistent with an increased impedance between the electrode and the endocardium which could be modified by changes in the patient's position.

Abrupt recovery of effective stimulation when a second nonenergized catheter was



Fig 1. Lung scan showing decreased perfusion in area of pleural friction rub.

passed into the right ventricle alongside the malfunctioning electrode might have resulted from the dislodgement of clot around the catheter tip or from a shift of electrode position. The virtually simultaneous occurrence of pleuritic pain followed by a pleural friction rub and enzymatic and isotopic evidence of pulmonary embolism and infarction are persuasive evidence that the second catheter sheared away a clot and restored electrical contact between the pacing electrode and the endocardium. We are aware of no previous instance of this form of pulmonary embolism.

The remarkable sequence of events included the development of a loud pleural friction rub within 1 to 2 hours after embolism occurred.

The subsequent failure of electrode pacing during cessation of heparin therapy with recovery of function upon reinstitution clearly suggests recurrent perielectrode thrombosis. The histologic identification of organizing clot about the extracted catheter lends credence to this possibility.

The effectiveness of Coumadin anticoagulation in this instance is suggested by the continued functioning of the pacemaker after heparin was supplanted by warfarin therapy.

Summary

In a case of pacemaker failure, insertion of a second transvenous electrode into the right ventricle resulted in apparent immediate pulmonary embolism and simultaneous restoration of effective stimulation by the original malfunctioning electrode.

The case provided an exceptional opportunity to recognize an offending perielectrode thrombus and to time precisely the sequence of events after pulmonary embolism. The effectiveness of anticoagulant therapy in preventing electrode interference by thrombosis was suggested.

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Review

The hydrogen ion and pulmonary vasomotricity

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Following the demonstration in 1950[1] that pulmonary hypertension is reversible in cor pulmonale due to obstructive lung disease, many investigators have implicated disturbed gas exchange as the chief cause of elevated pulmonary artery pressures. Other basic factors of possible importance in the genesis of this hypertension include (1) anatomic reduction of the size of the pulmonary vascular bed, (2) altered distensibility of the large elastic arteries of the lesser circulation, and (3) elevation of left heart or pulmonary vein pressures.

Although it cannot be denied that in these diseases there is anatomic reduction in the size of the pulmonary vascular bed, particularly of the capillary area, its role in the genesis of pulmonary hypertension must be very small in view of the following three observations. (1) Removal of 50 per cent of the vascular bed results in only slight pressure increase and this degree of vascular loss is probably larger than is usually seen in obstructive diseases. (2) Pulmonary hypertension in this form of cor pulmonale is reversible and therefore independent of anatomic lesions. (3) No correlation was found by Cromie[2] between the degree of lung destruction and evidence of right ventricular hypertrophy and dilatation at necropsy in thirty patients with bronchitis and emphysema.

A recent study by Harvey, Enson, and Ferrer[3] exonerates fully the large elastic arteries of the lungs from any contribution to pulmonary hypertension in these disease states. It is possible statistically to predict pulmonary arterial systolic and mean pressures as a function of stroke volume and pulmonary arterial diastolic pressure in normal subjects, an expression of large artery distensibility. If this relationship is unaltered in obstructive lung disease, i.e., if variations in stroke volume did not produce systolic and mean pressures higher than values predicted for normal subjects, then distensibility of the large elastic arteries is not abnormal in these states. Fig. 1 shows that the regression line relating predicted values of systolic pressure to that observed in patients with obstructive lung disease (solid line) is not different from the regression line (dotted) of normal

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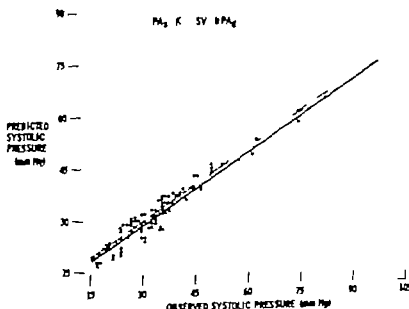


Fig. 1 Graphic representation of the relationship between the values for pulmonary arterial systolic pressure predicted from the equation $PA_s = K + aSV + bPA_d$ against those observed in 130 patients with obstructive lung disease. PA_d, pulmonary arterial diastolic pressure; PA_s, pulmonary arterial systolic pressure; SV, stroke volume; PA_s, values for systolic pressure predicted from the equation; K, a, and b are constants. The points indicate the values for systolic pressure predicted from the equation against the values observed in these patients. (From Harvey, Enson, and Ferrer: Bull. Physiopath. Respir. 3: 623, 1967.)

subjects. Thus, the effect of stroke volume on systolic pressure in these patients is not different from that in normal subjects and there is no reduction in the distensibility of the elastic arteries of these diseased lungs.

Left heart and pulmonary vein pressures, as measured directly or as reflected in the pulmonary wedge pressure, have repeatedly been found normal[4-7] in patients with cor pulmonale and pulmonary arterial hypertension. As seen in Fig. 2, a diastolic pressure gradient exists across the lung in these states and this gradient increases the greater the arterial oxygen unsaturation (Fig. 3).

Studies in normal subjects [10] and in patients without significant pulmonary vascular or mitral valvular disease[11] have shown that the pressure in the pulmonary artery is the same as that in the left ventricle at the end of diastole despite a wide range of blood flow and heart rate. These observations indicate that resistance to flow in the normal pulmonary vascular tree is negligible. The appearance of a pressure gradient can only be ascribed to an increase in resistance to flow. Indeed in patients with obstructive lung disease the magnitude of this diastolic pressure gradient correlates well with the classical calculation of pulmonary vascular resistance ($r = 0.919$, $p < 0.001$).[12]

Other investigators have demonstrated a rise in pulmonary arterial diastolic pressure without a concomitant rise in wedge pressure during acute hypoxia. Similarly we have found that acidosis, induced by infusions of hydrochloric acid (Fig. 4) produces an elevation of diastolic, mean and systolic pulmonary arterial pressures without changes in wedge pressure or stroke volume.[13] Thus, the gradient across the lung appears to be related both to hypoxia and to acidosis.

While left heart pressure can affect the level of pulmonary arterial blood pressure in this type of patient, as recently demonstrated by Segel and Bishop,[1] it does not contribute to this diastolic gradient as indicated by studies currently in progress in our laboratory. This condition is illustrated in Fig. 5. This 52-year-old woman with acute and chronic bronchitis had recently recovered from right ventricular failure. The administration of 500 ml. of

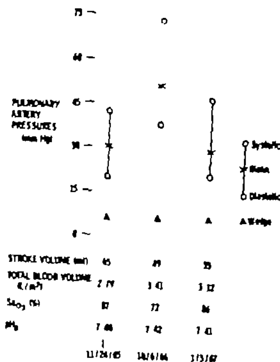


Fig. 2 Graphic representation of the hemodynamic findings in a patient with pulmonary hypertension due to obstructive lung disease before, during, and following recovery from right ventricular failure. Note that the pressure gradient between pulmonary artery diastolic pressure and the "wedge" pressure is greatest when the arterial O_2 saturation is lowest. Note that in the center panel when he was in *RV* failure, the gradient indicated by the shaded area, was large. At this time his arterial saturation and stroke volume were considerably reduced. When saturation rose, the gradient fell without change in wedge pressure. (From Harvey, Enson and Ferrer: B. IL. Physiopath. Respir. 3:623, 1967.)

dextran caused an increase in wedge and pulmonary arterial pressures and a slight increase in stroke volume. However the diastolic gradient across the lung decreased slightly. Thus, while the level of left heart pressures can influence the level of pulmonary arterial pressures, it cannot be held responsible for the diastolic gradient across the lungs. Rather this gradient is regulated by hypoxia and acidosis.

Returning now to the primary factors influencing pulmonary arterial pressures in obstructive lung disease, three variables must be considered: hypercapnia, hypoxia and hydrogen ion concentration.

Carbon dioxide retention is such a frequent finding in these patients with obstructive lung disease and pulmonary hypertension that it was originally postulated that molecular carbon dioxide might be a contributing cause to pulmonary hypertension. Hypercapnia has been variably reported to cause either a rise in pulmonary arterial pressures or no significant change in animals or in normal man. A slight rise in pulmonary arterial pressures was found in ten patients with emphysema who sustained an average increase of 7 mm. Hg in Pa_{CO_2} while breathing 3 or 5 per cent carbon dioxide.[8] This rise was ascribed to a concomitant increase of 15 per cent in cardiac output. The patients in our own series[11] who received sodium bicarbonate had an average rise in cardiac output of 32 per cent and an average rise in Pa_{CO_2} of 9 mm. Hg despite which pulmonary arterial pressure either fell or remained unchanged. The difference between these two studies was in the direction of change in blood pH. In those who inspired high carbon dioxide mixtures there was an average fall of 0.06 *pH* units, whereas in those receiving sodium bicarbonate there was an average rise of 0.09 *pH* units. These data suggest that carbon dioxide per se was not responsible for the changes noted in pulmonary arterial pressures, but that variation in hydrogen ion concentration was. Viles and Shepherd have recently suggested that carbon dioxide, far from being a pressor, may actually have a dilator effect on the vessel of the cat lung.

In 1946 Von Euler and Liljestrand proposed that a local decrease in alveolar O_2 tension would cause pulmonary vasoconstriction with consequent diversion of blood to better ventilated areas. Many investigators have confirmed this role of hypoxia in animals and man. In 1958, Liljestrand concluded that an increased hydrogen ion concentration is the chemical stimulus for this vasoconstriction. Noting that an increase in hydrogen ion in the circulating blood was associated with vasoconstriction in the pulmonary vascular tree, he pointed out that both hypoxia, by promoting release of lactic acid and retention of CO_2 will cause a rise in hydrogen ion concentration. He further suggested that the variability in pressure response to acutely induced hypoxia or hypercapnia may well be dependent not only on the net blood hydrogen ion concentration, but also upon local concentrations of hydrogen ion which in turn are influenced by vari-

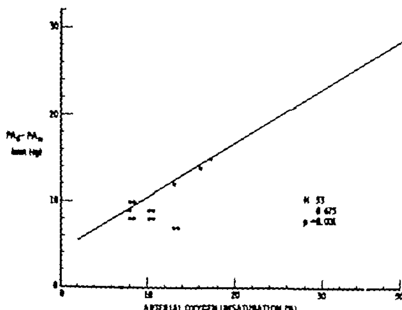


Fig. 3 Graphic representation of the relationship between the diastolic pressure gradient $P_A - P_{LA}$ across the pulmonary vascular bed and the arterial oxygen unsaturation (100 minus the arterial oxygen saturation). Note that the greater the unsaturation, the larger the gradient across the lung (From Harvey, Enson, and Ferrer Bull. Physiopath. Respir 3:623 1967)

ations in ventilation and perfusion

Our own investigations[12,13] as well as those of others[-40] have corroborated the vasomotor effects of variations in [H+] on the lesser circulation. Thus, changes in pH can potentiate or attenuate the response to hypoxia.

To test Liljestrand's hypothesis as it might apply to patients with disturbances in ventilation and in perfusion investigations on the effects of acute changes in pH were begun in 1959 by the authors. Acute alkalosis was induced with intravenous sodium bicarbonate and the amine buffer THAM[4] and acidosis by means of infusions of hydrochloric acid[13] Sodium bicarbonate caused a rise in pH and in pCO but the change in arterial saturation was negligible. Despite a considerable rise in pulmonary blood flow the pulmonary arterial pressures fell. THAM caused a rise in pH comparable to the bicarbonate study but had somewhat different consequences in that ventilation fell and arterial oxygen saturation rapidly reached levels such as one achieves with the inspiration of 12 per cent oxygen the pCO_2 remained unchanged. Despite the unsaturation or hypoxia and a rise in pulmonary blood flow pulmonary arterial pressures fell or remained unchanged Hydrochloric acid on the other hand inducing a fall in pH elicited a pressor response with no change in wedge pressure cardiac output, or pCO_2 and there was even a slight increase

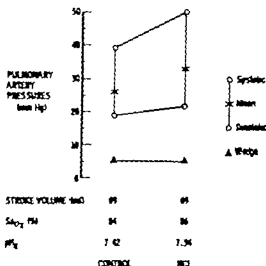


Fig. 4 Graphic representation of the effects of an infusion of 0.3M HCl on the pulmonary arterial blood pressure of patient with obstructive lung disease. Note that the gradient between the pulmonary arterial diastolic and wedge pressures increases as the blood pH falls. (From Harvey, Enson, and Ferrer Bull. Physiopath. Respir 3:623 1967)

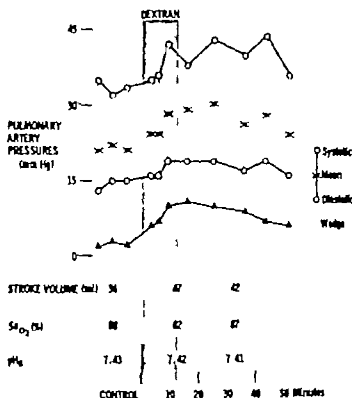


Fig. 5. Graphic representation of the effects of a rapid infusion of 500 ml. of dextran (shaded area) in a patient with obstructive lung disease. (From Harvey, Enson, and Ferrer: Bull. Physiopath. Respir. 3:623, 1967.)

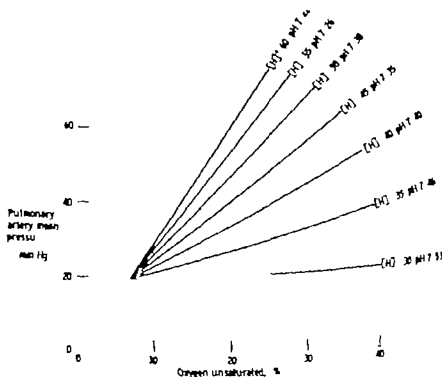


Fig. 6. Graphic representation of the relationship among *PA* mean pressure, arterial oxygen unsaturation, and hydrogen ion concentration. (From Enson, Giuntini, and Lewis: J. Clin. Invest. 43:1146, 1964.)

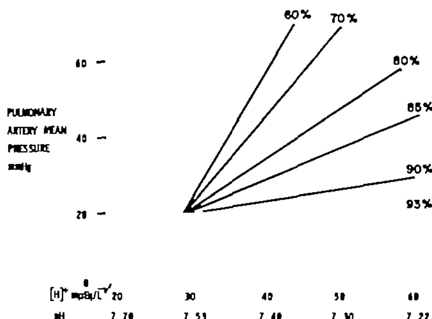


Fig. 7 Graphic representation of the relationship among *PA* mean pressure and blood hydrogen ion concentration and arterial blood saturation. (From Ferrer Bull. New York Acad. Med. 41 942, 1965.)

in arterial oxygen saturation. Summarizing these effects, one notes that pulmonary vasodilation occurred with a fall in hydrogen ion concentration during acute alkalosis despite conditions that usually provoke an increase in pulmonary hypertension namely a rise in cardiac output or a fall in arterial saturation or both. Pulmonary vasoconstriction was effected by a rise in hydrogen ion during acidosis.

Having convinced ourselves that both hypoxia and hydrogen ion concentration have an influence on pulmonary artery pressure and suspecting that they may be interacting stimuli an equation was developed relating the two stimuli hypoxia and hydrogen ion with pulmonary arterial pressures. The first graph (Fig 6) of this expression relates the interaction of the amount of arterial *unsaturation* (100 per cent saturation minus the actual saturation) using this as an index of alveolar hypoxia and blood hydrogen ion concentration in the production of pulmonary hypertension. It indicates that pulmonary mean pressure at low concentrations of hydrogen ion or high pH is relatively insensitive to hypoxia. As a corollary at minor degrees of unsaturation pressure is relatively insensitive to hydrogen ion concentration whereas it is extremely sensitive to this ion at high degrees of unsaturation. The second graph (Fig 7) presents this same relationship using the levels of arterial oxygen saturation as the isopleths. Again one notes the attenuating effect of normal or high pH values upon the pulmonary mean pressure in face of diminished arterial saturation For example at a saturation of 70 per cent (most patients with cor pulmonale due to obstructive lung disease have values between 60 and 80 per cent) with a pH of 7 42 mean pressure is 40 mm. Hg while at a pH of 7 30 it is 69 mm. Hg (see Figs. 6 and 7) These graphs can be employed clinically to predict the level of pulmonary hypertension using only information derived from an arterial blood sample in such patients and are accurate within 5 to 10 mm. Hg

Attempts to predict pulmonary arterial mean pressure in normal subjects or in patients with pulmonary disease whose arterial oxyhemoglobin saturation lies above 93 per cent have been unsuccessful This may be due to the lesser reactivity of the pulmonary vascular bed in normal

subjects or in patients without significant hypoxia.

This analysis indicates that pulmonary arterial mean pressure is related to arterial unsaturation and blood hydrogen ion concentration in a more complex fashion than a merely additive one One can speculate that the hydrogen ion and hypoxia are interacting stimuli one either facilitating or inhibiting the effect of the other on vascular smooth muscle The concept of dual stimuli is consistent with the hypothesis of Liljestrand if they both influence the production of intracellular lactic acid The site of action remains unknown it might be directly on the muscle cell or mediated by local receptors.

Recently Silove and Grover[83] and Hange[84,85] have shown that neither alpha adrenergic blockade tissue catecholamine nor serotonin depletion prevent the hypoxic pulmonary pressor response and therefore this vasoconstriction is not mediated through adrenergic receptor stimulation or release of serotonin or endogenous catecholamines. Endogenous histamine in the lung has been suggested[71,85] as a possible mediator in the pressor response.

Recent studies by Bergofsky and Haas[86] have selectively explored the possible anatomic site of action of the pulmonary vascular pressor response to hypoxia They applied the hypoxic stimulus separately at three sites alveolar precapillary or pulmonary arterial or postcapillary or pulmonary venous. They found no effect of hypoxia on the pulmonary veins and noted that the precapillary vessels (arteries about 1 mm in diameter) were the major site of constriction although isolated alveolar hypoxia (probably by local diffusion effects of the gases on the adjacent vessels) could also elicit such an effect The study suggested that the smooth muscle media of these arteries were directly sensitive to the hypoxic stimulus. A second study by Bergofsky and Holtzman[87] indicates that hypoxia has a depolarizing effect on the pulmonary arterial smooth muscle cell a membrane effect, so that it is closer to its excitatory threshold for production of an action potential and increased contractility and thus is more readily able to diminish the cross-sectional area of each vessel and the pulmonary vascular bed in general. Although such membrane effects exist they may not be the sole mechanism operating and they may be supplemented by other chemical pressor agents. More information at the cellular level is eagerly awaited in this particular problem of pulmonary hypertension.

Summary

A short review has been presented of the present state of knowledge regarding the relationship of the dual stimulation of the hydrogen ion and hypoxia on pulmonary artery vasomotricity These interacting stimuli are probably the major determinants of pulmonary hypertension in chronic obstructive lung disease

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Fundamentals of clinical cardiology

Geriatric cardiology

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Clinicians have long been aware that many diseases are modified by age and that certain diseases are even unique to elderly populations. Virtually all cardiovascular diseases as well as the response to therapy for these diseases are affected by age. Furthermore, the force of mortality increases with age, so that with advancing age death is produced by progressively less severe disease. The aged patient also has several to many diseases unrelated to the cardiovascular system but which modify his health and increase the force of mortality and which are causes for serious and often fatal independent or complicating illnesses. Because cardiovascular disease presents unique problems in the elderly, a geriatric cardiology clinic was established in 1965 at the Tulane University School of Medicine. This paper offers a brief survey of the nature of cardiovascular disease in the aged based upon our experience.

General considerations

Because aging does not proceed at a uniform rate in all individuals, there is no precise age which defines a geriatric population. However, problems related to aging appear in most individuals by the seventieth year, so anyone 70 years of age or older may be properly considered, at least for statistical purposes, as belonging in the geriatric age group. However, some individuals behave as if they were in the geriatric age group even before the sixth decade of life.

The clinical evaluation of elderly patients may be quite difficult. The history is often unreliable because of confusion, memory loss, or even senile dementia. A satisfactory physical examination may be difficult to obtain because of failure of the patient to understand commands or because of his lack of cooperation or inability to carry out simple diagnostic maneuvers. At times it is even impossible to obtain x-rays and electrocardiograms of good quality because of the patient's inability to cooperate and/or muscle tremor.

Even when the cardiovascular examination is satisfactory, there are unique problems in the aged, the most significant of which is what constitutes a normal arterial blood pressure. With increasing age there is loss of elastic tissue in the aorta and large arteries. This results in an increase in the rate of rise in pressure (decreased time of arterial upstroke), an increase in peak systolic pressure, and an increase in pulse pressure. The question is what level

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of arterial systolic blood pressure should be considered as normal. Although a definitive answer is not possible, we consider that an accurately recorded arterial systolic blood pressure greater than 150 mm Hg is abnormal. However, as discussed below, systolic arterial hypertension is not always treated in the elderly.

Another physical finding in the aged which may cause difficulty in interpretation is a basal systolic murmur. Sixty per cent or more of patients over 70 years of age exhibit an ejection type of systolic murmur at the base of the heart. In the overwhelming majority of such patients the murmur is hemodynamically insignificant. However, in a small number of patients significant left ventricular outflow tract obstruction is present. Radiation of the murmur into the neck or an associated thrill does not discriminate between significant and insignificant aortic stenosis. This problem will be considered in detail later in this paper.

A major difficulty in the evaluation of the elderly patient is that very often more than one disease is present. Chronic lung disease presents a particular problem since it is common in the elderly and is associated with dyspnea and orthopnea which are also symptoms of congestive heart failure. It must also be remembered that thyrotoxicosis seldom results in constitutional manifestations in the aged but is often associated with tachycardia, atrial fibrillation, and high output congestive heart failure. Peripheral edema is often due to poor systemic venous drainage, hypoproteinemia, and other factors common to the aged, such as reduction in skin tone and in tissue pressure, rather than to congestive heart failure.

Absence of symptoms of heart disease in elderly patients may be confusing and misleading. Because of immobility imposed by weakness, poor visual acuity, and arthritis, symptoms of heart disease which may have occurred if the patient were more active do not develop. The failure of the patient to complain of symptoms of heart disease may erroneously convince the physician that heart disease does not exist.

The influence of age on the electrocardiogram independent of heart disease is unknown. An increase in the P-R interval and atrial fibrillation are more common in normal elderly patients than in younger patients and probably reflect myocardial disease. We have observed an increase in notching and slurring of the QRS complex with aging. This finding is readily apparent in high frequency electrocardiograms as well as in the vectorcardiogram. Slurring of the QRS complex or deformity of the QRS sE loop[3] is found even in elderly patients whose hearts are considered to be normal at autopsy. It is likely that the increase in notching of the QRS complex reflects subtle physicochemical changes within the myocardial cell which are not apparent on routine autopsy examination nor even with existing chemical methods. We have previously postulated that electrically inactive cells may appear structurally normal and that such electrically silent cells may result in alterations of the QRS complex such as those observed in aging.

Radiographic interpretation, particularly in regard to heart size, may be difficult in the elderly. Because of anatomic changes in cardiac position secondary to chest deformity, the main pulmonary artery may appear enlarged. However, autopsy studies frequently do not confirm the existence of left ventricular hypertrophy or dilatation.

Cardiac disease in the elderly

Disorders of cardiac rhythm. Excluding premature contractions, the two most common disorders of cardiac rhythm in elderly patients are atrial fibrillation and ventricular tachycardia. Atrial fibrillation in elderly patients is of particular interest because it often occurs as the only electrocardiographic abnormality and may be seen in hearts which are considered structurally normal at autopsy. Nevertheless, detailed studies of the sinus node are not usually performed during routine autopsy examination. Such studies have indicated that the sinoatrial node undergoes progressive fibrosis with aging even in the absence of major disease of the coronary arteries. We have taught for many years that elderly patients with atrial fibrillation may lack a viable sinoatrial node and that attempts to convert atrial fibrillation to normal sinus rhythm with quinidine or

related drugs in these old patients may be hazardous. It is also of interest that atrial fibrillation often develops in elderly patients during even relatively mild infection. Although reversion to normal sinus rhythm may occur after the infection has run its course, it does not always occur. We have observed that atrial fibrillation develops more frequently during episodes of congestive heart failure in the elderly than in younger patients and that the development of atrial fibrillation in such patients is a poor prognostic sign. However, the salient point concerning atrial fibrillation in the aged is that it occurs in a significant number of patients without other clinical or electrocardiographic evidence of cardiac disease. On the other hand, ventricular tachycardia is often associated with ischemic cardiac disease and frequently occurs following acute myocardial infarction. In contrast to younger patients who may tolerate ventricular tachycardia for hours or even days, elderly patients develop congestive heart failure and/or cerebrovascular insufficiency soon after the onset of ventricular tachycardia. Thus, early and effective therapy to terminate ventricular tachycardia and to prevent its recurrence is essential.

Although complete heart block is a relatively frequent finding in elderly patients, it is surprisingly well tolerated. Only rarely has it been necessary to resort to cardiac pacing in patients over 70 years of age, whereas insertion of a cardiac pacemaker in younger patients with complete heart block is commonplace. It is probable that symptomatic patients with complete heart block either die before they reach 70 years of age or have had a pacemaker inserted before that time. Patients who do survive to the age of 70 without intervention have a sufficiently healthy cardiovascular system to compensate for complete heart block with a large stroke output. These considerations do not explain the apparent rarity with which complete heart block is observed to develop in patients more than 70 years of age. However, sudden death is frequent in old patients and some instances of sudden death are presumably due to the development of complete heart block. Observations on the coronary care unit indicate that the sudden development of complete heart block is catastrophic in old people and that attempts at artificial pacing are much less successful than in younger patients.

We have observed spontaneous paroxysmal atrial tachycardia (PAT) in only a few patients more than 70 years of age. In each instance it was well tolerated and not associated with aberrant intraventricular conduction. In one patient, she had PAT most of her life, the episodes appeared to come less frequently but they were more difficult to terminate as she grew older. Paroxysmal tachycardia secondary to digitalis intoxication is relatively common in elderly patients and is usually associated with aberrant conduction. However, this latter finding is also generally true for younger patients. The question of digitalis sensitivity in elderly patients will be discussed later in this paper.

Coronary heart disease. Ischemic or coronary heart disease is the most frequently occurring cardiac disease in the aged. It is well known that symptomatic coronary heart disease is about four times more common in men than in women in the fourth decade of life but that with aging the ratio narrows so that by 70 years of age coronary heart disease occurs almost as frequently in women as in men. The mortality rate from myocardial infarction in both sexes is three to four times higher in patients more than 70 years of age than in patients between 50 and 60 years of age. However, the survival rate following acute myocardial infarction is lower in elderly men than in elderly women.

The most important clinical findings in elderly patients with ischemic heart disease are the frequency with which myocardial infarction occurs without or with only minimal pain and the frequency of associated cerebrovascular stroke. Hypotension or shock, without pain, should always be attributed to myocardial infarction in the elderly. Although the incidence of painless myocardial infarction is relatively high in elderly patients, it may not occur as often as it is believed. Confusion, mental obtundation, and congestive heart failure may obscure anginal pain, particularly if it is not severe. Because of the possibility that a substantial number of elderly patients

with painless myocardial infarction may escape detection incidence and mortality statistics particularly those obtained from coronary care units, must be interpreted with caution.

It would appear that if a 50-year-old patient is alive 24 hours after the development of an acute myocardial infarction, there is a three to-one chance that he will survive. On the other hand the chances of survival unless meticulously managed, in a 70-year-old patient who is alive 24 hours after myocardial infarction are four to-one *against* survival. The high mortality rate in older patients following myocardial infarction is due to a number of factors, some of which are not directly related to the cardiac disease. Elderly patients are likely to have more advanced cardiac disease than younger patients. Congestive heart failure tends to be more severe and less responsive to therapy in elderly than in younger patients. The incidence of ruptured myocardium virtually always a fatal event, increases sharply with age Elderly patients are more likely to have associated diseases which limit the chance for survival than do younger patients. Thus, bronchopneumonia, chronic lung disease, urinary tract infection renal disease, cerebrovascular stroke and anemia may contribute to morbidity and eventually to mortality in the aged

Although serum enzyme changes following acute myocardial infarction occur with equal frequency in elderly and younger patients, classical electrocardiographic signs of myocardial infarction are less common in older than in younger patients. Failure of the electrocardiogram to reflect acute myocardial infarction in elderly patients is due, at least in part, to the high incidence of markedly abnormal electrocardiograms in this age group. Thus, the electrocardiographic manifestations of acute myocardial infarction must be superimposed upon the pre-existing changes of ischemic heart disease including those of healed myocardial infarction. The more abnormal the electrocardiogram the less likely it is to display the changes of acute myocardial infarction.

Although ischemic heart disease (with or without myocardial infarction) is the most common cause of congestive heart failure in the elderly it must not be assumed that all instances of congestive heart failure in the presence of normal arterial blood pressure in the elderly are due to coronary atherosclerosis. The diagnosis of ischemic heart disease must be made with the same care in old patients as it is in younger ones if other causes of heart failure in the aged such as thyrotoxicosis, anemia heart muscle disease (cardiomyopathy) and pulmonary heart disease are not to be overlooked

Many physicians are insensitive to or unaware of the many problems of medical care in the aged This is well illustrated by the fact that, in a patient 70 years of age or more who is admitted to a hospital and subsequently proven at autopsy to have suffered an acute myocardial infarction there is only a 50 per cent chance that the admitting diagnosis was acute myocardial infarction.

Hypertension As already mentioned there is no general agreement on the normal level of arterial blood pressure in the aged However it is well recognized that systolic and to a lesser extent, diastolic arterial blood pressures increase with age Although it is important from the statistical and actuarial point of view to establish limits of normal or expected blood pressure for the various age groups the clinician is not necessarily concerned only with the absolute level of blood pressure. Indeed the progressive increase in blood pressure which occurs with age is largely due to degenerative changes in the aorta and large arteries, which although part of the aging process, cannot be considered as normal Thus, although one may not be surprised to find an arterial blood pressure of 210/100 mm Hg in a 70-year-old individual one should not consider such a blood pressure normal merely because it is common We feel that an elevated systolic and/or diastolic arterial blood pressure should be lowered regardless of the age of the patient and whether or not symptoms of hypertension exist. However the physician should be careful to establish that the patient has true hypertension rather than transient hypertension due to emotional factors relative to the physical examination and the recording of the arterial blood pressure It is our practice

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Cardiopulmonary resuscitation Part II

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In the previous section the indications and patient selection for cardiopulmonary resuscitation (CPR) were discussed and techniques for proper ventilation and external cardiac compression were described. In all patients an intravenous infusion must be started either by a cut down or percutaneous puncture. The precipitating cause and immediate mechanism of cardiac arrest must be defined and treated when feasible

Cardiovascular mechanisms precipitating and occurring during arrest

Ventricular fibrillation The incidence of sudden death caused by ventricular fibrillation is not known but this arrhythmia is present in approximately one third of patients first seen in cardiac arrest and is particularly common during acute myocardial infarction. A firm blow to the chest or institution of external cardiac compression infrequently may cause reversion to a regular rhythm. However electrical countershock, producing sudden depolarization of the entire heart, is the only efficacious method for defibrillation. Although some investigators consider DC shock superior to AC shock, both methods effectively depolarize the heart. Ventricular fibrillation may persist despite repetitive electrical shocks particularly when fine fibrillatory waves are present on the electrocardiogram Studies in the dog and clinical results in man have shown that an intracardiac injection of epinephrine 0 3 to 0 5 ml. (1 1 000 solution) may produce large fibrillatory waves (coarse fibrillation) facilitating electrical defibrillation The intracardiac administration of lidocaine (50 to 100 mg) either alone or with epinephrine may aid electrical defibrillation in refractory cases.

A brief period of asystole commonly occurs after defibrillation and restoration of an effective spontaneous rhythm may not occur immediately If no pulse is palpable or blood pressure is inadequate external cardiac compression must continue during this period Patients with ventricular fibrillation complicating congestive heart failure, acute pulmonary edema or shock have a less favorable prognosis than those with ventricular fibrillation occurring without these conditions. Epinephrine should be given cautiously following conversion of ventricular fibrillation However many episodes of ventricular fibrillation attributed to epinephrine may be secondary to hypoxia or acidosis.

Following termination of ventricular

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fibrillation or ventricular tachycardia anti arrhythmic drugs should be administered to prevent a recurrence Lidocaine is the preferred agent and is given as a 1 to 2 mg per kilogram bolus followed by a continuous infusion of 1 to 4 mg per minute Intravenous procainamide or quinidine can be used but hypotention and myocardial depression may occur If the ventricular arrhythmia was induced by digitalis toxicity and recurs despite lidocaine diphenylhydantoin 3 mg per kilogram given slowly intravenously may be useful Sustained ventricular tachycardia can effectively be treated by countershock or lidocaine Bretylium tosylate may aid in prevention and treatment of ventricular arrhythmias, but its role in clinical therapy remains to be clarified. Recently atrial or ventricular pacing usually by a transvenous route, either alone or in combination with drugs (propranolol lidocaine procainamide) has been efficacious in controlling recurrent ventricular tachyarrhythmias.

Asystole and bradycardia When ventricular asystole is present a firm precordial blow may initiate cardiac action If this is not successful an intracardiac injection of epinephrine 0 3 to 0.5 ml of a 1 1 000 solution should be given and external compression resumed This procedure may produce an adequate cardiac rate Epinephrine may convert asystole to ventricular fibrillation which can then be terminated with countershock An intracardiac injection of isoproterenol 0 02 to 0 04 mg or calcium chloride 3 to 10 c.c. of 10 per cent solution followed by external compression may also initiate a heart beat. Isoproterenol is often effective in treating complete heart block with slow idioventricular or nodal rhythms A continuous infusion of isoproterenol at a rate of 1 to 4 μg per minute will usually maintain a satisfactory heart rate Atropine 1 to 2 mg given intravenously with elevation of the legs is effective when hypotension is present with sinus bradycardia or a slow nodal rhythm With asystole or marked bradycardia, external pacing may be tried but it is frequently ineffective.

With recent techniques, transvenous endocardial pacing can be rapidly instituted at the bedside Percutaneous puncture of either subclavian vein is made and a semifloating electrode catheter is advanced to the right atrium or ventricle using electrocardiographic monitoring for determining the catheter position. An external power unit is used for pacing. Capture of the ventricle with stable pacing has been achieved in an average of less than 20 minutes, and within 5 minutes in 30 per cent of patients. If asystole or an ineffective heart rate persists despite drugs and attempts at emergency transvenous pacemaking direct transthoracic needle puncture into the right or left ventricular cavity should be made. A bipolar or unipolar pacemaker wire is then passed to the endocardium and pacing is initiated. There are few reports of effective results with this latter method perhaps because of delay or myocardial and coronary artery injury Recovery is rare with total cardiac standstill, even if pacing is employed

Shock If shock is present, vasopressor drugs such as metaraminol or levarterenol can increase systemic arterial pressure and myocardial contractility resulting in better coronary artery perfusion and cardiac output. When the cardiac rate and rhythm are adequate but a low cardiac output and blood pressure persist, agents with positive inotropy can restore circulation. Digitalis calcium chloride isoproterenol norepinephrine, and recently dopamine or glucagon produce increased myocardial contractility with variable effects on blood pressure. Combinations of these drugs can act synergistically to increase cardiac output arterial pressure, and urine flow In normotensive man dopamine 2 to 6 μg per kilogram per minute has been reported to produce less arrhythmias and chronotropic effects than isoproterenol 0.01 to 0.16 μg per kilogram per minute. Further studies of dopamine effects during shock are needed particularly with larger doses (10 to 20 μg per kilogram per minute) Glucagon may also be a useful agent. The mode of action in producing increased contractility is unknown, but it is independent from that of digitalis. The dose used is 5 mg per kilogram repeated every 30 minutes or 100 mg per minute as a continuous infusion Since calcium chloride

potentiates certain effects of digitalis, it should not be administered when digitalis toxicity is suspected

Often the heart rate may be adequate with the sinus node, a lower cardiac focus or even an electrical pacemaker controlling the heart, but cardiac output remains ineffective even after full doses of inotropic and vasopressor drugs This state is often referred to as electrical mechanical dissociation the heart muscle is regularly depolarized, but no effective contraction occurs. The prognosis is almost always fatal.

Acidosis

The reduction in circulation during cardiac arrest decreases tissue perfusion which results in hypoxia anaerobic metabolism and rapid formation of lactic acid Metabolic acidosis with elevated lactate and depressed plasma bicarbonate concentrations develops in most patients during cardiac arrest. In the majority of patients, pH concentrations before therapy have been less than 7.25 with improvement occurring during resuscitation A normal oxygen saturation and a normal or decreased carbon dioxide tension frequently is present following resuscitation. In patients with underlying pulmonary disease pulmonary edema, aspiration or inadequate ventilation, carbon dioxide retention with hypercapnea and respiratory acidosis occurs. In these patients severe acidosis (combined metabolic and respiratory) and hypoxia are common. Acidosis prevents effective resuscitation because it depresses myocardial contractility produces loss of intracellular potassium decreases cardiac and peripheral vascular responses to catecholamines, lowers the threshold for ventricular fibrillation and may induce cardiac asystole

Treatment of acidosis consists of adequate ventilation restoration of circulation, and administration of alkali. Sodium bicarbonate is the drug of choice for correcting the metabolic acidosis. Sodium lactate produces less base initially and must be metabolized for further effect. Tris buffer (THAM) offers little advantage and is not recommended. Various regimens for bicarbonate therapy based on patient weight or duration of arrest have been suggested If the arrest has lasted less than 15 to 30 seconds, with rapid recovery and no prior acidosis, base is usually not needed For more prolonged periods of arrest 50 (44.6 mEq) to 100 ml of sodium bicarbonate is given intravenously immediately followed by 50 ml every 5 to 10 minutes during the resuscitation In published reports, an average of 150 to 250 mEq of bicarbonate has been needed to correct the metabolic acidosis. Alkalosis has been produced by overadministration of bicarbonate but usually is not clinically significant These doses are only a general guide to bicarbonate therapy because the precise base deficit occurring during circulatory arrest is impossible to determine Therefore the initial doses are empirical but later accurate determination of bicarbonate dosage should be based on serial observations of plasma bicarbonate concentration and blood pH

Electrolyte disturbances Hyperkalemia has become a more common cause of cardiac arrest, particularly since the increased use of aldosterone antagonists and potassium supplements. Hyperkalemia should be suspected as precipitating cardiac arrest in patients receiving these drugs, or in patients with renal insufficiency Hyperkalemia can often be detected from the electrocardiogram Treatment consists of intravenous sodium bicarbonate glucose and insulin and a cation-exchange resin such as sodium polystyrene sulfonate (Kayexelate) given orally or by enema.

Hypokalemia can cause serious arrhythmias and cardiac arrest, especially in patients receiving digitalis. Treatment with potassium is indicated for tachyarrhythmias associated with a low serum potassium. When a bradycardia is present, administration of potassium may depress the cardiac pacemaker further and even produce asystole. In these instances the heart must be electrically paced prior to the use of potassium.

Recent evidence has shown that following cardiopulmonary bypass, during chronic diuretic therapy or with diabetes mellitus hypomagnesemia may occur Administration of magnesium sulfate following cardiopulmonary bypass has aided defibrillation in resistent cases and may be of value in other instances when hypomagne

semia is present. Other electrolyte imbalances may develop and should be corrected.

Indications for discontinuing CPR

The best criteria used in evaluating the effectiveness of CPR are pupillary size and light reactivity, level of consciousness, and occurrence of spontaneous movement, respirations, or heart beat. The decision to discontinue CPR is frequently difficult and may have medicolegal implications. Few reliable standards are available to indicate that further resuscitative efforts are hopeless or that permanent neurologic damage will exist despite successful resuscitation.

Pupillary constriction to light indicates adequately oxygenated blood flow to the brain. A dilated pupil that reacts to light is associated with brain hypoxia, but pupillary reactivity indicates that return of function is possible. A dilated, fixed pupil for 15 to 30 minutes is indicative of cerebral death. Funduscopic examination that reveals disruption, fragmentation, and random movement ("railroading") of blood within retinal vessels correlates with brain death. The electroencephalogram (EEG) is usually not available, but it can be helpful. An isoelectric (equipotential, flat) EEG sustained for more than one hour (2 to 3 hours in children) during normothermia, even with satisfactory ventilation and circulation, invariably signifies cerebral death. However, without adequate cerebral circulation, even brief periods of an isoelectric EEG portend irreversible cerebral damage. Prolonged deep unconsciousness, absent reflexes, lack of spontaneous respirations or cardiac activity for 30 to 60 minutes further reflect biological death. When these criteria for brain death are met, further resuscitative efforts are futile and indeed may produce a patient with only a vegetative existence.

Care after resuscitation

Care after resuscitation has not been adequately emphasized. Approximately two thirds of patients successfully resuscitated will die before being discharged from the hospital. Recurrent arrest is frequent in the immediate survivors and indicates not only the severity of the underlying pathology, but the need for further improvement in therapy. All patients who have been resuscitated should be placed in an intensive care unit or an area where similar facilities for proper monitoring and attention are available. The primary disease process and possible cause of the arrest should be evaluated and vigorously treated. Complications of CPR mentioned before should be looked for and corrected. Adequate ventilation and circulatory support must be maintained. A tracheotomy may be indicated if an endotracheal tube still remains after 48 hours, and if continued assisted ventilation is needed. Continuous electrocardiographic monitoring with rapid correction of arrhythmias is mandatory. Frequent determinations of vital signs must be made. If the patient has recently had ventricular tachyarrhythmias, a continuous lidocaine infusion (1 to 4 mg per minute) should be administered. Marked bradycardias are usually best treated by electronic pacing.

Monitoring the central venous pressure is a useful parameter for evaluating the cardiac and circulatory status, particularly during shock. An abnormally high or increasing venous pressure may indicate the need for diuretics or inotropic drugs, while a falling or low pressure may require volume loading for correction. Serial determinations of arterial pH, pCO_2, and pO_2 are indicated, especially in patients with congestive heart failure, shock, or pulmonary disease. Serum electrolytes should be obtained and urine output measured. Cerebral edema may be decreased by hypothermia, urea, or steroids, and further neurologic damage prevented, but existing anoxic changes will not be reversed. The period after resuscitation should be one of anticipating complications, which unfortunately are frequent, particularly recurrent cardiac arrest.

Results and prognosis

The survival rate following CPR is variable, depending upon the hospital area where the arrest occurs, the basic disease process, and complications. Successful resuscitation is significantly greater in the operating room, recovery room, intensive care unit, and cardiac catheterization laboratory than in other hospital areas, largely due to immediate recognition of the arrest.

availability of personnel and equipment, and possibly to less seriously ill patients. In the operating room and in the immediate postoperative period, long term survival with closed and open-chest techniques averaged 29.5 per cent in over 1 100 patients. In these same areas with open chest techniques alone 29 per cent of another 1 710 patients survived. Long term survival was 25 per cent in a combined series of 1,270 patients resuscitated externally in all areas of a hospital However in 2,155 patients reported since 1961 without acute myocardial infarctions who had cardiac arrest outside the operating room or cardiac catheterization laboratory externl resuscitation was initially successful in 30 per cent, but only 13.3 per cent of the total (individual series range 3 to 22 per cent) lived to be discharged. Initial successful external resuscitation occurred in 3? per cent of 508 patients reported in the literature with acute myocardial infarction and cardiac arrest, but only 10.3 per cent of all the patients (series range 4 to 22 per cent) survived to be discharged

Recent reports from intensive care areas indicate a significant decrease in mortality rates, mainly due to prevention and prompt therapy of life threatening arrhythmias particularly ventricular fibrillation. However pump failure remains a formidable obstacle to successful resuscitation. The mortality rate approaches 100 per cent when cardiogenic shock severe congestive heart failure, repeated arrests, or uremia complicate the clinical course. Despite these observations, the result of resuscitation in any individual case is not predictable. Although further studies are needed available data concerning long term survival after hospital discharge appears encouraging with many patients living months to years following discharge.

Future developments

Mechanical failure of the heart during cardiac arrest is a major cause of death Recent developments in techniques and equipment for mechanically assisted circulation have opened a new encouraging era. Since the viability of the patient must be maintained by continuous resuscitation rapid and easy implementation of the mechanical device is necessary Unfortunately this facility has not been fully developed due to a need for better materials, techniques and experience. One mechanical method is counterpulsation (arterioarterial pumping) which utilizes a catheter that removes blood from the central arterial system during systole and returns it during diastole. This device decreases the left ventricular work, but rapid blood movement may cause hemolysis and precise pressure monitoring is needed Limited clinical experience with counterpulsation has not been particularly fruitful

Intra aortic balloon pumping is performed by passing a catheter balloon retrograde from a femoral artery to the descending thoracic aorta. The balloon is inflated during diastole with carbon dioxide or helium and deflated during ventricular systole An augmented diastolic pressure and an increased coronary artery flow occu Despite inherent dangers of balloon ruptu e and incorrect phasing good results have been reported in a few patients with shock.

Left heart or partial cardiopulmonary bypass with an extracorporeal pump and oxygenator may be the desired therapy in a cardiac arrest not espond ng to usual techniques. However the time required to place the patient on the pump the duration of pump time and the lack of immediate availability of personnel limit its use In the near future more advances may obviate these difficulties.

It has been estimated that 50 pe cent of patients with an acute myocardial infarction die before hospital admission most from a cardiac arrest secondary to an arrhythmia. Formation of a highly mobile resuscitation team (flying squad) that goes to patients homes when a diagnosis of an acute myocardial infarction is made may decrease mortality Further development and implementation of this concept is indicated since a significant decrease in mortality rate is possible by early detection therapy and prevention of cardiopulmonary arrest, particularly secondary to life-threatening arrhythmias.

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Annotations

Pathophysiology and treatment of orthostatic hypotension

When man assumes the upright position, various neuromuscular and endocrine systems are activated to maintain blood volume, venous return to the heart, cardiac output, arterial blood pressure, and circulation to vital organs. The normal response to standing includes reflex arteriolar and venous vasoconstriction, acceleration of heart and respiratory rates, release of norepinephrine, activation of the renin-angiotensin system, and increased secretion of aldosterone and antidiuretic hormone.[1-7] Inadequate function of these regulatory mechanisms may cause blood pressure to decrease and symptoms of impaired cerebral circulation to develop.

Orthostatic hypotension appears as a complication of many diseases which affect components of the blood pressure regulating system. Accordingly, when blood pressure decreases abnormally with standing, studies should be done to exclude adrenal-cortical insufficiency, hypopituitarism, hypothyroidism, diabetes mellitus, primary amyloidosis, and porphyria. Neurologic diseases which affect the autonomic nervous system, such as posterior fossa tumors, Wernicke encephalopathy, brain stem lesions, and tabes dorsalis also should be considered. After all of these recognized causes have been excluded, a diagnosis of idiopathic orthostatic hypotension usually is made. This syndrome includes, in addition to orthostatic hypotension, other manifestations of disturbed autonomic nervous system function. Heart rate usually is fixed, reflex vascular responses to body warming and cooling are exaggerated, and reflex venomotor activity is impaired. Other common findings include impotence, anhydrosis, impaired bowel and bladder function, decreased synthesis and abnormal metabolism of norepinephrine, and exaggerated vascular responses to infused vasopressors. In addition, small changes in blood volume cause wide swings in blood pressure, indicating that vascular responses to volume stimuli are not normal.

Sodium metabolism, which may be abnormal in patients with orthostatic hypotension,[10-14] is of special interest because alterations in sodium balance greatly modify blood pressure and symptoms in these individuals.[10, 14-17] Impaired renal sodium conservation may result from diminished tubular sodium reabsorption, particularly when the patient assumes a recumbent position.[16] Moreover aldosterone excretion sometimes is reduced and unresponsive to stimulation, suggesting that orthostatic hypotension is caused by hypoaldosteronism, with renal salt wasting and hypovolemia.[18] This concept of pathogenesis could explain why administration of sodium chloride and salt-retaining steroid hormones increases blood pressure as sodium and water balances become positive, and body weight and chloride space increase. However, hypoaldosteronism and renal salt wasting do not account for the development of orthostatic hypotension in most cases. Renal salt wasting cannot always be demonstrated, and usually is not severe. When present, it may be accompanied by normal aldosterone excretion, and may persist despite administration of desoxycorticosterone acetate (DOCA).[19] Moreover, treatment with sodium chloride and salt-retaining steroid hormones is beneficial in patients with normal aldosterone excretion and in others with no (or only minimal) renal salt-wasting.[14] These observations indicate hypoaldosteronism and renal salt wasting may complicate, but do not necessarily cause, orthostatic hypotension.

Treatment of patients with orthostatic hypotension has included application of elastic stockings, elevating the head of the bed, and administering ephedrine or other vasopressor substances.[20] These approaches, which occasionally offer relief in mild cases, are ineffective in patients with severe symptoms. Treatment designed to expand plasma volume by increasing body sodium content is more beneficial. When patients with orthostatic hypotension are given sodium chloride, sodium balance becomes positive, body weight increases, and blood pressure and symptoms improve somewhat.[15] Administration of salt-retaining steroid hormones, such as

Table I. Effect of sodium intake on response to Florinef in a patient with orthostatic hypotension

Sodium intake (mEq/24 hr)	Florinef (2 mg./24 hr)	Blood pressure upright (mm./Hg)	Symptoms (0-4+)
10	No	30/10	4+
10	Yes	34/10	4+
200	Yes	96/70	0

Table II Response to tilting in a patient with orthostatic hypotension

P rameters	*Salt depleted symptomatic*		*Salt loaded asymptomatic*	
	Recumbent	*Tilted 4 min*	*Recumbent*	*Tilted 4 min*
Brachial arterial pressure (mm Hg)	110/73	73/50	143/95	137/75
Cardiac index (L./min./M)	3 1	2 7	3 3	2 8
Total peripheral resistance (dynes/cm ⁻⁵)	1,360	1 100	1 780	1,550
Plasma olume (liters)	2 7		3 2	
Blood volume (liters)	4 6		5 2	

fludrohydrocortisone (Florinef), results in significantly greater positive sodium balance and additional increases in blood pressure which in some cases are striking These responses to Florinef are seen only if sodium intake is maintained. It is ineffective when given during period of dietary sodium deprivation (Table I).

Patients treated with salt and Florinef may improve even though the abnormal autonomic vascular responses persist. In one case reflex arteriolar vasoconstriction after body cooling was delayed and erratic, and reflex asodilation in response to body warming wa exaggerated when blood pressure was low during period of salt depletion. These abnormal vascular reactions persisted after the patient had become asymptomatic following treatment. In another case (Table II) hemodynamic responses to tilting were bnormal both before and after blood pressure had been increased by salt and Florinef administration.

Patients nable t maintai normal blood pressure when standing should be studied with respect to the etiology of their orthostatic hypotension. Renal sodium conservation and aldosterone secretion also should be evaluated. Treatment then should be initiated by increasing dietary salt content or by administering sodium chloride tablets. If symptoms persist, Florinef should be added while the high sodium intake is maintained. Additional salt supplements may be req ired temporarily if excessive amounts of sodium are lost through sweating or gastrointestinal disturbances. In most patients with orthostatic hypotension, whatever the cause, symptoms can be alleviated and standing blood pressure maintained by administering Florinef and carefully ttending to dietary sodium content and external sodium losses.

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Hepatic dysfunction associated with renal transplantation

The increased susceptibility to infections in patients receiving transplanted organs and immunosuppressive therapy is well recognized.[1-3] In these patients steroids and azathioprine are generally the basic immunosuppressive agents. However, when a rejection episode is diagnosed the doses are increased and other agents may be included. Jaundice complicating renal transplantation was observed by Straffon and associates. The development of "hepatitis in intermittent dialysis units can be a serious complication of therapy"[1, 4] and in the absence of a definite causative agent this is usually considered to be of viral origin. The virus may be transmitted via blood transfusion or during dialysis. Wyatt and associates[4] and Carlstrom and co-workers[2] have reported hepatitis associated with cytomegalovirus infection, the inclusions of which are often found in postmortem studies of renal transplant patients.

The clinical course and biochemical and necropsy findings of five patients who after cadaveric renal transplantation developed disordered liver function have been described by Evans and associates. All patients were prepared by hemodialysis or peritoneal dialysis, and after transplantation, all needed hemodialysis. Multiple blood transfusions were given. Basic immunosuppressive therapy with prednisolone and azathioprine was used, and in addition to extra steroids in four patients, antirejection therapy included actinomycin C in two, antilymphocytic globulin in two, and extracorporeal irradiation in one patient. One patient had abnormal serum glutamic pyruvic transaminase prior to transplantation and another had hepatosplenomegaly. Four of the five patients developed jaundice, drowsiness, and asterixis and three lapsed into coma before death. One patient had no clinical signs of liver dysfunction although transaminase levels were raised. Two other patients in the unit at the time were jaundiced but this subsided. One of these patients died seventeen months later.

The morphological appearances in the livers of all patients who died included increased liver cell pleomorphism, increase in mitotic figures in liver cells, bile duct proliferation with occasional bile plugging and necrosis of liver cells. The zones of necrotic liver cells ranged from groups of a few cells to large foci involving several lobules. Similar focal necrosis was also seen in the livers of seven of eleven other patients with renal allografts from the same unit. Increase in portal tract connective tissue occurred in two patients. In none of the livers was there a substantial inflammatory cell infiltrate. In four patients cytomegalovirus inclusions were present in various tissues including the liver and this virus was cultured from lung tissue in one of these cases. Liver tissue from two patients was cultured but no cytomegalovirus was grown.

The morphological features in the liver are not those generally associated with viral hepatitis[4] or cytomegalovirus infection. Standard doses of azathioprine have been shown to be hepatotoxic to normal dogs. It is possible that in these patients because of poor renal function higher blood levels of azathioprine than those normally achieved were present and that these higher serum levels could be hepatotoxic. However, in view of the clinical features the liver morphology possibly represents the accumulative effect of more than one hepatotoxic agent. The recognized hepatotoxic factors in these patients include the virus of infective hepatitis, the cytomegalovirus, and a range of drugs including azathioprine.

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Assessment of the immediate prognosis during acute myocardial infarction

The success of coronary care units in treating serious arrhythmias has emphasized the importance of estimating the immediate prognosis during acute myocardial infarction. Until recently clinical prognostic indices, which take into consideration the previous history of the patient, age clinical features, complications, and gross differences in electrocardiogram pattern, have provided the only immediate means of assessing the severity and prognosis of any particular episode of infarction.[1-4] They are of very limited value since they underestimate the importance of arrhythmias and fail to take into account the changing pattern of risk according to the time after onset of symptoms. The clinical state of patients alters rapidly after acute myocardial infarction and accurate allocation of a prognostic score is difficult and unreliable. Moreover the experience of coronary care units has shown that ventricular fibrillation or asystole can occur in patients whose prognostic score is low

While a large infarct usually carries a poorer prognosis than a small one, extent of infarction is not necessarily an index of immediate vulnerability to serious arrhythmias and, neither the electrocardiogram nor serum enzyme levels provide reliable means of assessing the degree of damage in the earliest stages of the clinical episode. Even serum creatine kinase levels, which rise earlier than other serum enzymes, seldom reach maximum levels before 16 to 18 hours. A simple method of assessing the vulnerability of the patient within 12 hours of the onset of symptoms is needed and should permit therapeutic measures on a selective basis before serious arrhythmias, ventricular failure, or shock develop.

The most important advance towards this end has been the continuous monitoring of the electrocardiogram. Ventricular tachycardia and frequent multifocal or R-on-T ectopic beats predispose to ventricular fibrillation, and suppression of these ventricular arrhythmias can be expected to reduce its incidence. The gradual development of increasing degrees of heart block can lead to asystole, which can often be effectively treated by electrical pacing. Even the sudden onset of asystole or complete heart block in patients with anterior myocardial infarction should not be unexpected if bundle branch block is also present.

Attempts to identify measurements which point

in screening of the clinical state have centered on correlating changes in plasma constituents with arrhythmias and sudden death. Biochemical changes known to be associated with the electrical stability of the myocardial cell have been most extensively studied. Changes in potassium levels in the plasma have not provided a useful index, but metabolic acidosis and low pH levels have been claimed to be useful prognostic indicators in severe infarction.[5,6] Increased levels of urinary[7] and plasma[15] catecholamines occur after acute myocardial infarction, and a close correlation may exist between elevations of catecholamine levels and deterioration in clinical state. However, catecholamine levels are of limited value as an immediate prognostic index. Plasma cortisol levels are also elevated[9] but no significant correlation between the degree of elevation and prognosis has been established.

Respiratory function studies, especially the measurement of PaO_2,[10] and its response to oxygen therapy have shown that the degree of arterial desaturation may be a useful prognostic index—especially if the patient shows clinical evidence of shock and acute left ventricular failure. More recently, the measurement of central mixed venous oxygen saturation has been advocated as an objective measurement of the clinical state,[12] and persistent lowering of the $CVSO_2$ may indicate a poor prognosis.

Recently, we have reported that serum free fatty acids (FFA) are elevated soon after acute myocardial infarction, and their level correlates directly with the incidence of serious arrhythmias and sudden death. When levels above 1,200 μEq per liter were observed, the immediate prognosis was poor. Serum FFA levels cannot be judged from the clinical state of the patient or the extent of myocardial damage as shown by enzyme levels, and they may be elevated in the uncomplicated patient who later suddenly and unexpectedly develops ventricular fibrillation. The reason for this association is not clearly understood at the moment; the increase in serum FFA and serious arrhythmias could both result from excessive catecholamine activity or alternatively high levels of FFA in the ischemic myocardium could themselves lead to arrhythmias.[16] Potentially, the serum FFA level is a particularly useful early guide to prognosis since the increase occurs, unlike changes in serum enzymes, during the first hours and when arrhythmias are still common. Its value as an immediate prognostic index is, however, limited by the time taken to complete the analysis. If the results can be made available quickly there is a case for treating patients with levels above 1,200 μEq per liter with antiarrhythmic drugs.

More work is needed. We must have a quick and reliable index of immediate prognosis to enable preventive treatment to be applied selectively and effectively. This must be available when the patient is first seen.

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Estrogens and puerperal thromboembolism

Pulmonary embolus is now second only to abortion of maternal death in England and Wales nd 70 per cent of these deaths occur in the puerperium. The reports on Confidential Enquiries into Maternal Deaths in England and Wales[1-4] have consistently shown that increasing age, parity and cesarean section have marked effect on the incidence of deaths from pulmonary embolus. Similar findings have also been described by individual investigators.

A fourth etiologic factor was suggested by the findings whole population study in Cardiff for 1965 and 1966. All single deliveries were divided into parity groups (0 1+2 3 and 3+), into two age groups (under 25 years, 25 years or older), and into spontaneous or other type of delivery the latter including cesarean section. The patients were classed as lactating or nonlactating according to the method of feeding on the seventh puerperal day. The exact method of suppression of lactation was not recorded but over 80 per cent of the deliveries were conducted in hospital and stilbestrol was used at that time by all the Cardiff hospitals. The dose ranged from 30 to 60 mg. daily for three days, followed by 20 to 30 mg. daily for the next three days, and 10 mg. daily for the final three days. All the cases of thromboembolic complications who had had lactation suppressed had received stilbestrol. Thromboembolism was defined in the study as any case of pulmonary embolism or deep vein thrombosis with signs definite enough to indicate the use of anticoagulants.

There were 44 cases of thromboembolism in 9,324 deliveries (incidence 4.7 per 1,000). Of these 9,324 patients the method of feeding was not known in 33. The study confirmed the increased risk with increasing age, parity and following operative delivery but the method of feeding was also seen to influence the incidence even when these other factors were taken into account. In 3,064 lactating women there were 7 cases of thromboembolism (incidence 2.3 per 1,000), whereas in 6,227 nonlactating women there were 37 cases (5.9 per 1,000). The eight cases of pulmonary embolism (one fatal) all occurred in the nonlactating group (1.3 per 1,000).

There was marked difference in the two age groups. Of 4,260 mothers under 25 years old, only 9 had thromboembolic complications (2.1 per 1,000) compared with 35 in the 5,031 mothers in the older age group (7.0 per 1,000). In the younger age group suppression of lactation had no effect on the incidence of thromboembolism, but women over 25 years had an increased risk in all parity groups if lactation had been suppressed. There were 1,201 lactating mothers of 25 years or older of parities 0, 1 or 2 who had one thromboembolic episode (0.8 per 1,000), whereas in 2,137 mothers of similar age who were not lactating, 19 had thromboembolic complications (8.9 per 1,000). In mothers having their fourth or subsequent child who were over 25 years old, the incidence of thromboembolism in the lactating group was 5.9 per 1,000 compared with 10.1 per 1,000 in the nonlactating group.

Mothers who had had an assisted or operative delivery were at increased risk this being accentuated if lactation had been suppressed. The incidence for all spontaneous deliveries was 4.3 per 1,000 compared with 8.2 per 1,000 following other deliveries. Lactating mothers who had a normal delivery had an incidence of thromboembolism of 2.6 per 1,000 those not lactating 5.1 per 1,000. Following assisted or operative delivery there were no cases of thromboembolism in lactating mothers, but in those who were not lactating the incidence was 12 per 1,000.

The over-all figures were found to be statistically significant, indicating that suppression of lactation was factor in the etiology of puerperal thromboembolism. The difference between the two groups was not due to difference in distribution by parity, age, or incidence of operative delivery nor could it be explained by difference in factors such as previous history of thromboembolism, anemia, or complications of pregnancy labor or the puerperium.

Others have since reported similar findings. Hill and Wilson[5] used data from the *Hospital Inpatient Enquiry* and compared the incidence of thromboembolic complications following live and stillbirths. It is reasonable to assume that most of the patients delivered of a stillbirth would have had lactation suppressed, and the incidence of suppression of lactation following live-births at that time was about 35 per cent.[10] Following 157,433 live-births, they found 777 cases of thromboembolism (4.9 per 1,000), whereas following 3,169 stillbirth deliveries there were 32 cases (10.0 per 1,000). Their findings differ from those of other series in that there was a marked difference in incidence (2.2 per 1,000 following live-births to 6.6 per 1,000 following stillbirths) in women under 25 years old, but in the other age, parity and method of delivery groups, their findings were very similar to those of others. Jeffcoate and associates[11] described the findings in 111 consecutive cases of puerperal thromboembolism. The estrogen used in their hospital group was ethinylestradiol. Their findings are similar to those of the Cardiff survey except that the overall incidence was lower

(1.2 per 1,000) and that women under 25 who had had an assisted or operative delivery had an increased incidence of thromboembolism if they had also been suppressed. They emphasize the very high risk of thromboembolism in patients over 35 years who has had an assisted or operative delivery and has been suppressed, the incidence being 34 per 1,000 as compared with 3.6 per 1,000 in similar lactating patients. The series of 25 cases described by Millar and Robertson is of interest because the dose of stilbestrol used was considerably less than that in Cardiff (a total of 110 mg.). The over-all incidence of puerperal thromboembolism was lower (1.6 per 1,000) but this is unlikely to be due to the difference in dosage of stilbestrol as there was marked difference in incidence in the lactating and nonlactating groups (0.5 and 3.0 per 1,000, respectively). One series[6] so far has been published where there is no evidence that suppression of lactation increased the risk of thromboembolism.

Doubt has been cast on the reality of the relationship[2,5] between suppression of lactation and puerperal thromboembolism because of the fact that the maternal death rate from pulmonary embolism has continued to drop[1-4] despite great increase in suppression of lactation in recent years. There has been many changes in obstetric practice during this time, however, which may be tending to lessen the incidence of thromboembolism. These include the probably increased use of anticoagulants and the decreased incidence of postpartum hemorrhage, anemia, and prolonged labor. The tendency toward childbearing at an earlier age, coupled with more efficient limitation of family size, further complicates the epidemiology. Another factor that has to be taken into consideration and is being investigated at present is the possibility that in the United Kingdom the increase in artificial feeding has been mainly in young women and unpublished data on the Cardiff population supports this possibility. Despite this real decline in mortality rate, a retrospective study by Ministry of Health assessors into the method of infant-feeding in 85 women who died of puerperal thromboembolism for 1961 through 1966 showed that 57 (67 per cent) had received estrogens. The significance of this finding will depend on the incidence of lactation suppression in the country at the time of these deaths, and is likely to support the evidence that the suppression predisposes to thromboembolism as only about 30 per cent of women in England and Wales were suppressed in 1962 and 40 per cent in 1964 and 55 per cent in 1966.

The pathogenesis of venous thrombosis is still not understood but it is likely that changes in venous blood flow, vessels, platelet function, and the coagulation and fibrinolytic systems play a part. Changes have been shown to occur in all these factors in the puerperium and also following estrogen administration. The description of markedly raised factor IX plasma level in the puerperium only in those patients who had received stilbestrol is however the only published work in which the effect of estrogen administration on any of the factors mentioned above, has been assessed during the puerperium. It was found that while the mean plasma value for factor IX in 43 lactating women (132 S.E.M. ± 6.6) was identical to that in late pregnancy the mean value for 48 women who had lactation suppressed with stilbestrol was markedly raised (187 S.E.M. ± 6.8) to above the normal range in normal nonpregnant adults (90 to 100 per cent). Twenty women who had lactation suppressed without the use of drugs had a mean factor IX value of 143 per cent (S.E.M. 9.1 ±). Further work[12] has shown that in 15 women receiving hexestrol for suppression, the mean value was 174 per cent. This difference between estrogen and the nonestrogen groups is statistically highly significant.

A possible clinical significance of this finding is suggested by the work of Wessler and Reimer. They showed that factor IX, together with factors XI and XII plays an important part in the production of serum-induced venous thrombosis in animals. It is possible, however, that the factor IX activity measured in serum by these workers, may differ from the factor IX activity measured by us in plasma in the presence of kaolin. Further work by Wessler and his colleagues[17] is of interest in this context in that they have shown that liver function affects the susceptibility of the animal to serum-induced thrombosis. It is known that oral contraception,[18] stilbestrol, and ethinylestradiol,[19] but not progestogens alone,[18,19] decrease the hepatic excretion of bromsulphthalein into the bile while apparently increasing liver blood flow. It is possible that the estrogen content of the contraceptive pill, stilbestrol, and ethinylestradiol produce a prothrombogenic[7] ... [20] situation by their effect on the liver, the change in factor IX plasma levels being a reflection, possibly an important reflection, of this effect.

The findings described in this annotation suggest that the use of estrogens in situations where they are of doubtful value[21,22] should be reassessed.

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NOTICE.—Beginning in January 1970, abbreviations for journal titles in references are to follow the style used in the Cumulated Index Medicus. These abbreviations may be found in the Subject Index of the Cumulated Index Medicus, as well as in the publication entitled *List of Journals Indexed in Index Medicus* published by the National Library of Medicine and available at a nominal price from the Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. 20402.

Book reviews

Handbook of Pediatric Cardiology. By L. Jerome Krovetz, M.D., Ph.D., Ira H. Gessner, M.D., and Gerold L. Schiebler, M.D., Hoeber Medical Division, Harper & Row Publishers, New York, 1969. 353 pages. Price $16.50.

This handbook briefly summarizes the pertinent clinical problems of pediatric cardiology. The authors describe in Part I the fundamental aspects of clinical cardiology, namely applied anatomy, embryology, genetics, hemodynamics, physical examinations and history taking, electrocardiography, vectorcardiography, etc. In Part II the specific diseases are discussed. In less than 400 pages the book obviously cannot be complete, but it is intended to be a small book for beginners in pediatric cardiology and for those who are interested in the essentials of cardiology in infants and children. This handbook should be especially useful for those who plan to practice pediatrics.

Pulmonary Blood Volume in Health and Disease. By Paul N. Yu, M.D., Philadelphia, 1969, Lea & Febiger Publishers, 314 pages. Price $15.00.

Dr. Yu has gathered into a single volume some of the most important present day concepts in pulmonary blood volume in man. He reviews the history, methodology, controlling mechanisms, and the influence of normal physiologic states and diseases on pulmonary blood volume. He failed, however, to indicate to the reader the inaccuracies of methods used for measuring blood volume. It is this which has handicapped and in fact delayed significant observation of important normal and abnormal physiologic phenomena which influence pulmonary blood volume. Dr. Yu does an excellent job in reviewing and recording existing concepts and data, but fails to do this critically for the beginner in cardiovascular and pulmonary research. Nevertheless, in spite of these quantitative limitations, the book is a good one. The qualitative data and the relatively grossly accurate quantitative data are extremely useful. The finer points in pulmonary circulatory physiology will be clarified as the sensitivity of techniques improves.

The book consists of five sections and eighteen chapters. Methods, levels of pulmonary volume in normal man, in the presence of valvular and myocardial disease, and physiologic and pharmacologic factors which influence pulmonary blood volume are among the many aspects of the problems discussed. This book should be useful to cardiologists, cardiovascular physiologists, and those working in cardiac catheterization laboratories. The book is well written, adequately illustrated, and well supported by good references.

A Treatment Manual for Patients with Pulmonary Emphysema. By Alvan L. Barach, M.D., New York, 1969, Grune & Stratton, Inc., 101 pages. Price $4.95.

This manual on the management of pulmonary emphysema summarizes in less than 100 pages the experience and recommendations of an expert. Dr. Alvan Barach is well known to pulmonary physiologists and clinicians. His ideas are clearly presented in this manual. The illustrations are effective and the bibliography includes a large part of the author's own bibliography on emphysema. The manual is directed primarily toward therapeutics.

Electrocardiography for the Anesthetist. By W. N. Rollason, M.B., M.R.C.S., D.A., F.R.A.R.C.S., Philadelphia, 1969, F. A. Davis Company, 147 pages. Price $5.25.

This small book, as the title indicates, briefly summarizes the use of the electrocardiogram for anesthetists. The author does this very well. The use of electrocardiography in medicine is increasing constantly, especially in the operating room. Anesthetists can make use of these recordings to advantage in many ways. As ECG technicians throughout the world learn to interpret by constant association with ECG recordings, so can anesthetists. Rollason has made available a useful book for them. The second edition includes two new chapters, one on the use of the ECG in intensive care. The book should encourage the readers to study ECG more extensively and to study books that describe the principles of the ECG more thoroughly. This is a useful book for anesthetists and nurses.

The Surgery of the Common Congenital Cardiac Malformations. By Christiaan N. Barnard, M.D., M.Med. (Cape Town), M.S., Ph.D. (Minnesota), F.A.C.S., F.A.C.C., and Velva Schrire, M.Sc., Ph.D., M.D. (Cape Town), F.R.C.P.E., F.R.C.P., F.A.C.C., New York, 1968, Hoeber Medical Division, Harper & Row Publishers, 179 pages. Price $5.95.

This brief monograph adds very little new to the publications already available on this subject. The authors present their opinions and approaches which are sound and conventional. The conciseness and clarity of the presentation is the main virtue of the book. Those who wish to review quickly the congenital defects of the heart and the surgical procedures offered for their management will find this book to be useful.

THE MICROCIRCULATION A Symposium. Edited by William L. Winters, Jr M D and Albert N Brest, M D Springfield, Ill., 1969 Charles C Thomas, Publisher 195 pages.

This book consists of papers presented at a symposium on the microcirculation held in Philadelphia on March 10 and 11 1966. The presentation includes discussions of the functional anatomy and physiologic considerations of the microcirculation, the capillary wall, and regional studies and disorders of the microcirculation. The papers are well selected to include some of the pertinent material on rheology cinemicrography capillary permeability and neurovascular control of the pulmonary circulation, among other aspects of the problem. Some of the contributors are outstanding investigators who have had considerable experience with problems of the microcirculation. This book should be of value to physiologists, students, and investigators who are concerned with the peripheral circulation

LA CINÉANGIOGRAPHIE SÉLECTIVE DES ARTÈRES CORONAIRES. By G La nure and F Rijtano, Paris, 1968, L'Expansion Scientifique Française, 114 pages.

This short manual summarizes the techniques, interpretations, and application of cineangiography of the coronary arteries in clinical practice. Although there are no new ideas to be found in the manual, the authors have gathered in a single volume the pertinent aspects of the subject for the reader The anatomic and pathologic relationships of coronary artery disease to the clinical states of ischemic heart disease are well presented. Like others who write on the subject, the authors have not emphasized the limitations and difficulties. The photographs of the angiograms are not uniformly clear They reveal the inadequacies of this technique to those who know the extent of and importance of the role of smaller vessels in the nourishment of the myocardium. Nevertheless, this is a useful noncritical monograph of about 100 pages on cine-coronary angiography

ELECTRICAL ACTIVITY OF THE HEART Edited by G W Manning Ph.D M D F.R.C.P.(C) F.A.C.C., F.A.C.P and S P Ahuja, M B B.S., D.T.M & H (Eng) F.R C.P.(C) F.A.C.C., Springfield, Ill., 1969 Charles C Thomas, Publishers, 341 pages. Price $15 00.

This publication contains the proceedings of a symposium held in London, Ontario, from May 24 to 26 1967 The participants were almost entirely from the United States and Canada. The subjects discussed were rather extensive. The presentations were grouped into six parts concerned respectively with cellular electric activity of the heart, the spread of excitation, disturbance of the electrical activity of the heart, electrical control of arrhythmias, display methods of electrocardiography and computer analysis of the electrocardiogram. These proceedings include many important and well-presented aspects of electric activity of the heart. Those who follow the medical literature carefully will find little if anything new whereas those who do not will find this to be a very good publication to study and own. These papers clearly indicate the complexities of bioelectric phenomena and the relative crudeness of the methods employed to study them Nevertheless, the clinical usefulness of routine electrocardiography in spite of its extremely rough nature, cannot be denied. The introduction of electron microscopy emphasizes the need for even more refined and elegant techniques for studying the electric activity of the heart. The papers presented in this book summarize very well the present state of knowledge concerning important selected aspects of bioelectric phenomena of the heart. This book is recommended to students and cardiologists.

BALLISTOCARDIOGRAPHY AND CARDIOVASCULAR PERFORMANCE. Proceedings of the Thirteenth Annual Meeting of the Ballistocardiograph Research Society held at Atlantic City N J May 4, 1968 Edited by Isaac Starr Basel, 1969 S. Karger, 115 pages. Price $6.95

This publication represents primarily the proceedings of the meeting of the American Ballistocardiographic Research Society held in Atlantic City on May 4 1968. Nineteen papers concerned with various aspects of ballistocardiography are presented. They deal with theory mechanics, diagnosis, and aspects of therapeutics of cardiac diseases. Those employing ballistocardiography and studying the subject should find this a useful book to own.

Books received

ANTIBODIES AND IMMUNITY By C J V Nossal, New York, 1969 Basic Books, Inc., 238 pages. Price $5.95.

HANDBUCH DER MEDIZINISCHEN RADIOLOGIE. ENCYCLOPEDIA OF MEDICAL RADIOLOGY VOL IX, PART 2. Edited by L. Diethelm O Olsson, F Strnad, H. Vieten, and A. Z ppinger New York, 1969 Springer Verlag Berlin, 466 pages. Price $55 00.

HEIDELBERGER TASCHENBÜCHER BAND 48 MEDIZINISCHE DIAGNOSTIK—GRUNDLAGEN UND PRAXIS By Dudolf Gross, New York, 1969 Springer Verlag, 218 pages. Price $2.45

INTERNAL MEDICINE IN WORLD WAR II—VOL III INFECTIOUS DISEASES AND GENERAL MEDICINE. Editor in Chief Col. Robert S. Anderson, Editor for Internal Medicine W Paul Havens, J Washington, D C., 1968, Department of the Army Office of the Surgeon General, 778 pages Price $8 25.

MANUAL OF MEDICAL THERAPEUTICS—19TH EDITION Editors J y W Smith, Boston, 1969 Little, Brown & Company 391 pages.

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Editorial

Detection and treatment of anxiety in the coronary care unit

T. P. Hackett, M.D.
N. H. Cassem, M.D.
Howard Wishnie, M.D.
Boston, Mass.

There are few physicians who would challenge the notion that fear or anxiety should be kept at a minimum in the patient occupying a coronary care unit (CCU) bed. At the same time few of us would question the coronary patient's cause for some apprehension or concern even though he is receiving excellent intensive care.

Recent work[1] has demonstrated that 40 out of 50 patients from a coronary care unit gave some evidence of being anxious. They admitted feeling anxious, requested reassurance about their condition, asked for sedation or appeared tense, fidgety or hyperactive. Thirty two of 50 patients occupying individual rooms in a private CCU displayed similar anxiety. In neither of these groups was anxiety extreme. It was rare to find a patient who spontaneously complained of nervousness or who appeared apprehensive to the casual observer. This lack of complaint perhaps explains why 20 patients in the first group and 12 in the second were undersedated. We used the presence of anxiety as described above as our operational definition of undersedation. Thirteen patients in the first group and 7 in the second were given insufficient sleeping medication. The complaint of insomnia was our sole criterion for undermedication for sleep. With these figures in mind it comes as no surprise that one out of 10 patients in the first group were given insufficient medication for the relief of pain. Although these figures may seem unreasonably high, we doubt that they would differ significantly in most CCUs about the country.

Two factors share the responsibility for unintentional undermedication. First is the failure of the patient to express the need for sedation. The patient fails to communicate either verbally or nonverbally that his state of mind is unsettled or nervous. Second is the failure of the physician to observe anxiety in patients who are reluctant to reveal it.

Let us consider the first point in more detail. In our culture, particularly in the lower socioeconomic groups, being nervous, even with good cause, is considered a weakness. Such patients do their best to hide fear, perhaps in the belief that denying it will somehow lessen the feeling. The denial of fear is commonly found in coronary care units.[1] This method of denial can take many forms. One patient may simply pre-

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tend to be calm even though he is mortally frightened underneath while another enjoys a seemingly gratuitous calm which actually is the end result of a complicated and unconscious series of mental mechanisms. An example of the more complicated form is the case of a 52 year-old engineer who maintained an insouciance disquieting to his physician during his hospitalization for myocardial infarction The doctor finally asked his patient why he was so cheery The reply was that his father had suffered his first myocardial infarction at 52 and lived comfortably twenty more years. Having *his father's constitution* assured his ability to survive It was not until weeks after his discharge home that he remembered a paternal uncle who succumbed to coronary disease in his early fifties This revelation produced a sudden episode of panic He clearly saw how a trick of his mind had blinded him to reality in the service of perpetrating a fear reducing fiction. The thought that the myth of invulnerability might have been punctured while he was acutely ill made him shudder Another patient remained quite calm throughout his stay in the hospital only to lapse into a nervous depression after reaching home. He told us that he literally did not experience fright anytime in the hospital because despite what he was told he believed his diagnosis to be subdeltoid bursitis rather than a myocardial infarction. The bursitis had pained him for two years prior to the onset of his coronary symptoms which were quite similar in severity and distribution to his bursitic pain Throughout his hospital stay he was able to maintain the conviction that a misdiagnosis had been made. That ability vanished once he reached home and experienced angina and dyspnea. When anxiety replaced tranquility he longed to be able to deny fear as he had in the hospital but found no way to do so A third patient who maintained an air of doughty confidence while on the unit later admitted that he had been terribly apprehensive, particularly after witnessing a fatal cardiac arrest but had been even more fearful of revealing his fear lest he lose control altogether

The first two cases exemplify a group of patients we refer to as major deniers. These are people who categorically deny being frightened at any time in the course of their illness. Generally their denial does not end after discharge as happened in the cases cited. Nineteen major deniers were found in the ward group 8 in the group of private patients. They usually demonstrate a lifelong pattern of denying fear and often use fatalistic clichés ("When you gotta go, you gotta go) to explain their attitude We prefer to regard them as individuals with an unusual ability to deny being frightened rather than to accept their lack of fear at face value. We do this because fear or some reasonable concern is so appropriate for the person struck down with acute coronary disease that its total absence would indicate either a profound depression in which death is desired or an impairment in reality testing of psychotic proportion Since our patients were neither psychotic nor suicidally depressed, we assumed that fear although not admitted, was present but somehow channeled elsewhere shelved perhaps in the patient's unconscious. We predicted that measuring the galvanic skin response and the biochemical indicators of emotional stress would disclose the presence of fear on an autonomic level We are in the process of testing this prediction but have insufficient data to support an opinion.

The second factor responsible for undermedication requires a certain amount of self-scrutiny on the part of the physician. Perhaps it requires some additional training as well. The doctor usually accepts the presence of anxiety with the aid of (1) the patient who either complains directly of anxiety or indirectly reveals its presence by asking for sedatives (2) objective signs of anxiety such as restlessness, overbreathing, worried facies, and excessive perspiration (3) a third party such as a spouse or nurse who informs the doctor that his patient is anxious (4) empathy—the doctor deems his patient anxious because he would be were he in that patient's place These are all reasonable ways of establishing the presence of anxiety in patients, but neither singly nor in combination do they insure a correct answer

Our data as well as the findings of others[?] point out that it is most unusual to find a CCU patient who complains of anxiety or requests additional sedation The objective

ages of anxiety occur in direct proportion to the degree of emotional distress. Consequently short of severe apprehension or panic, which are uncommon in CCU's one must either be unusually sensitive to the physical manifestations of anxiety or be willing to scrutinize the patient's behavior over long periods to detect these signals of underlying fear Opinions provided by relatives are always prejudiced and unless the doctor knows his informant well they should not be trusted Nurses are excellent sources of information about anxiety because patients are apt to be less guarded with them than with doctors. Furthermore the nurse is constantly with the patient and has the opportunity to see him in a variety of moods. However nurses need to be taught what to look for Otherwise they tend to be too subjective in their assessment. The physician more through training in medical school than by personal preference is inclined to dismiss empathy and distrust intuition As a consequence potentially valuable instruments of diagnosis remain, for the most part unused

If the standard methods for diagnosing anxiety fail in the CCU how should the internist proceed? Is there a special technique for uncovering anxiety in patients who contrive to conceal it? There are of course, various psychological tests designed to do this type of job but with few exceptions, they have no place in the setting of intensive care. The technique we use has nothing special about it We simply ask each patient if he is frightened

Most physicians view this direct approach with suspicion. They are understandably hesitant to suggest, through a question that their patient's situation ought to be frightening There are, however ways of phrasing a question without offering a threat. After rapport has been established hopefully early in the interview we ask our patient how he responded to the first signs or symptoms of the infarction. We always inquire whether the pain or dyspnea frightened him We explain that many people experience fear and that this is quite normal. We then proceed to a discussion of their current situation in the CCU and give examples of patients we have known who did not care for the monitor and other machinery We go on to say that annoyance or even fear is not unusual but rather a normal response to being confined in the unit With this approach we attempt to reduce whatever tendency the patient has to equate fear or anxiety with weakness or cowardice Our method of inquiry has met with no complaints, but the results are not especially rewarding because over 90 per cent of the patients in both groups, ward and private deny fear when asked the first time in this context The longer we spend with each patient the more he is apt to admit having been afraid or even being afraid but the amount of time required to elicit the information is more than the usual internist would be able to give

This being the case what can be done to simplify the recognition of the anxious patient in the CCU? In point of fact there is very little that can be done With the amount of time available to the internist or cardiologist an attempt at differentiating the truly anxious patient from the calm would probably result in as many misses as hits It is far better to assume that all patients are anxious to some degree and treat them routinely for it If the proper drugs are used in correct doses the principle side effect will be no more than drowsiness which can be reduced by adjusting the dose or changing the drug

A variety of sedatives and tranquilizers are employed in coronary units. These can be broken down into three categories barbiturates, substituted phenothiazines, and diazepines. Phenobarbital, the perennial all purpose sedative is being used less frequently because of its cumulative effect and tendency to dull mentation Pentobarbital amobarbital and secobarbital are commonly employed as hypnotics. Their use in standard doses offers no particular hazard to the cardiac patient. Although their use may markedly decrease the plasma half life of Coumadin, this poses no problem in management as long as the prothrombin time is monitored so that the dose can be adjusted

Chlorpromazine perhaps the most widely used substituted phenothiazine, is the preferred agent when heavy tranquilization is needed Its use in either oral or parenteral form should be re[illegible] those patients who exhibit [illegible] ere[illegible] or im-

pending delirium If the patient is kept at bed rest, the hypotensive effect of this drug carries little risk. Thus far the only direct cardiotoxic effect of the phenothiazines, such as sudden death with intramyocardial lesions, have been reported[6] in patients receiving very large daily doses.

Chlordiazepoxide in oral doses of 10 to 20 mg four times a day and diazepam given orally in doses of 5 to 10 mg four times a day are widely used minor tranquilizers which are both effective and safe when administered to patients with a recent myocardial infarction We have employed them routinely in our CCU[1] and have encountered no adverse reactions. It has been reported[7] that chlordiazepoxide can intensify anger in patients who exhibit both anxious and angry behavior Although we have not as yet observed this response it may be advisable to choose diazepam rather than chlordiazepoxide in patients with a history of irritability or quick temper

Another point must be kept in mind for the effective use of sedation in coronary units. Orders that are written for p.r.n use rarely serve their purpose Perhaps because patients in these units receive such excellent care as standard fare they are hesitant to make additional requests. Asking for a tranquilizer may be seen as an admission of weakness. Whatever the reason it has been our experience that p.r.n orders for sedatives in the CCU are seldom taken in therapeutic amounts. This observation finds corroboration in the works of Davis.[8] It is more effective to order the medication on a routine basis and adjust the dose if the patient should require more or less.

There is a tendency especially in sedating cardiac patients, to allow concern about possible side effects to eclipse the primary purpose for administering the drug While it is true that all sedatives and tranquilizers may tend to lower blood pressure and some to depress respiration as well except for the unpredictable idiosyncratic response, side effects are for the most part trivial and incidental when compared to the potential benefit the drug can provide

A discussion of this sort would be incomplete without mentioning the second most common emotional reaction to myocardial infarction depression Twenty-eight patients in each group showed signs of being depressed but none seriously enough to consider using antidepressant medication. It has been our experience that depression is more apt to pose a problem in management when the patient leaves the hospital and attempts to resume a more normal way of life. Since the tricyclic antidepressants, which are generally regarded as the best drugs for this condition have cardiovascular effects[9] they should be avoided if possible in the CCU and employed with caution during convalescence If depression becomes so severe that treatment is mandatory electric convulsive therapy has been used successfully on patients with severe heart disease.[10,11] In this situation the patient was monitored continuously throughout the modified convulsion and defibrillating equipment was close at hand

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Clinical communications

Detection of left atrial thrombi

Scintillation scanning after administration of ^{131}I rabbit antibodies to human fibrinogen

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The presence of left atrial thrombi may be clinically suspected and subsequently confirmed by angiocardiogram The detection requires either right heart or left atrial catheterization followed by injection of contrast media. In the majority of cases satisfactory opacification of the left atrium can be achieved by the injection of a bolus of contrast media in the pulmonary artery This technique has been routinely employed in many laboratories when left atrial thrombi are strongly suspected to preclude the possibility of dislodgement of the thrombi and embolization in the systemic circulation by transseptal left atrial catheterization However cardiac catheterization can cause considerable discomfort to the patient and may also involve untoward side effects as sequelae to the manipulation of the catheter as well as reactions to the contrast media.

Earlier studies with ^{131}I labeled anti

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bodies to fibrin demonstrated that this preparation would concentrate in areas of deep venous thrombi and that this deposited radioactivity could be detected by scintillation scanning techniques and give clinically useful information[3] As part of this latter study scanning was done on one patient with a left atrial thrombus after intravenous injection of ^{131}I labeled antihuman fibrin A zone of increased radioactivity was found in an area corresponding to the left atrium Subsequent examination of the surgically removed thrombus revealed that there was 9 times more radioactivity in portions of the clot than in an equal weight of blood

To determine the clinical usefulness of ^{131}I labeled antifibrin antibodies to detect atrial thrombi 30 consecutive patients scheduled for mitral valve surgery under cardiopulmonary bypass were injected with the ^{131}I preparation scanned several days later and underwent operation soon thereafter Samples of mitral valve atrial appendage blood and thrombi whenever obtained were counted and relative ^{131}I concentrations were calculated

Methods

The techniques of antibody purification and iodination have been described in detail elsewhere[3-4] and they are summarized as follows. Antiserum from rabbits immunized with human fibrinogen was added to citrated human plasma and clotting was induced by the addition of calcium and thrombin After centrifugation the clots were homogenized and washed with buffer The clotbound antibody was eluted with pH 11 6 solution and this one-time purified antiserum was then dialyzed overnight against a borate buffer The resulting preparation was incubated at 37° C with human fibrin which had been prepared by clotting citrated plasma homogenizing the clot and treating it with pH 11 6 buffer to remove soluble components. After one hour the mixture was centrifuged and the washed residue containing antibody bound to fibrin was eluted at pH 11 6 The supernatant, referred to as twice-purified antiserum was dialyzed overnight against borate buffer

Four milligram portions of this antibody were iodinated by the ICl method To this procedure was added in rapid succession by jetting procedure 2 ml. of 4 7 × 10⁻⁴ M ICl followed by ^{131}I which had been brought to pH 8 with concentrated borate buffer One minute later 2 ml. of 6.25 per cent human albumin were added as a protective protein The radioactive preparation was passed through Dowex 1 M resin contained in a 2 ml syringe and rinsed with an additional 1.5 ml. of albumin Radioactive iodine determinations, using an NaI crystal scintillation counter were performed on the effluent and resin to determine the percentage of iodination. This was generally 45 to 50 per cent when 250 mc. of ^{131}I was used

After a two-hour dialysis against sterile physiologic saline the iodinated preparation was passed through a sterile millipore filter system for sterilization and subsequently diluted with 3 per cent human albumin The resultant preparation approximately 100 ml. containing 1 mc. per milliliter was dispensed in 5 to 15 ml. aliquots into sterile vials and frozen until used

An aliquot of each labeled sterile diluted preparation was used for assay of in vitro clotability This was done by mixing the ^{131}I preparation with citrated human or rabbit plasma forming a clot by the addition of calcium and after centrifugation determining the percentage of the added radioactivity that reacted with each clotting system In general between 70 to 75 per cent of the ^{131}I preparation was found in the human clot and less than 5 per cent in the rabbit clot Such tests were repeated on such preparations after freezing and thawing with no differences found in the per cent clotability Other preparations were labeled with 1 to 2 mc of ^{131}I and reacted similarly with the clotting human and rabbit plasmas. It would thus seem that there is little if any damage done to the antibody either as a result of ^{131}I labeling with 250 mc. or due to freezing after labeling

Skin tests with 0.1 ml. of normal rabbit gamma globulin (35 γ per milliliter) were done on all patients 10 to 15 minutes before the radioactive preparation was given. The radioactive preparation was given intra

Albumisol, Merck, Sharp & Dohme, West Point, P

venously at a dose of 6 μc per kilogram of body weight. No positive reactions were seen nor were any untoward symptoms or signs related to the diagnostic study. The patients were also given 10 drops of Lugol's solution orally at the time of radioisotope administration and three times daily for 5 to 10 days to block accumulation of the catabolized ^{131}I in the thyroid.

The patients were scanned 1 to 5 days later using a Picker Magna-Scanner with a 5 inch focusing 276 hole coarse collimator and a 5 inch sodium iodide crystal. Scanning speed was 30 to 40 cm. per minute. Anteroposterior and occasionally posteroanterior views of the chest were done. The results were recorded on paper using colorcoding and also on film.

One to two days after the scan or 2 to 7 days after the ^{131}I antibody injection, the patients underwent mitral valve surgery. Surgical specimens were obtained from the operating room, weighed, and counted in a NaI-well scintillation counter. All calculations were done relative to an injection standard.

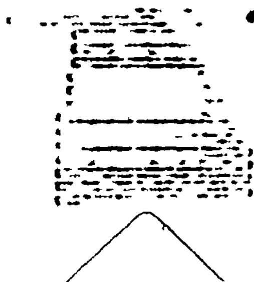


Fig. 1. Results of scan performed on patient 3 days after intravenous infusion of ^{131}I antibody to human fibrinogen. At surgery the next day no thrombus was found in the left atrium.

Results

Altogether 30 studies were done on 29 patients. Twenty-five patients had mitral valve replacement, 3 had mitral commissurotomy, and 1 patient underwent the operative procedure twice, once for mitral valve replacement and two months later for resuturing of the valve. Both studies on this patient were included. For the sake of simplicity we consider that the data were obtained from 30 patients.

On the basis of the paper and photo scans, a tentative diagnosis of the presence or absence of a left atrial thrombus was made. Of the 30 patients, 26 were diagnosed as having no left atrial clot. A photoscan of a typical normal heart is shown in Fig. 1. The greatest concentration of radioactivity was in the ventricles and is substantially less in the atria. This reflects the relative blood volumes in these chambers since the greatest portion of the ^{131}I antibody is present in the blood and is similar to the scans one obtains with ^{131}I labeled human serum albumin. At operation, no thrombus was found in the left atrium in all but one patient, (Table I, Patient 23). This exceptional patient had a large organized

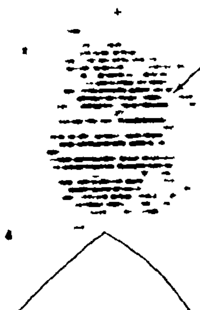


Fig. 2. Results of scan performed on Patient 4 (Tables I and II) two days after intravenous infusion of ^{131}I antibody to human fibrinogen. The arrow points to an area of increased radioactivity corresponding to that of the left atrial appendage. At surgery the next day a thrombus was removed from this position.

thrombus in the left atrium which did not have a very large accumulation of 131I in most areas.

In the remaining 4 patients on the basis of the scans the presence of left atrial thrombi was strongly suspected. At operation three patients had thrombi whereas the fourth patient had a very calcified mitral valve. Fig. 2 shows a scan that demonstrated an increased I concentration in the region of the left atrium that is consistent with the presence of left atrial thrombus. The relative amount of radioactivity in this area is somewhat greater than that found in the ventricles. Two days later a thrombus in the left atrial appendage was found (Patient 4). Fig. 3 shows a scan obtained from another patient. There is an increase in radioactivity in the atrium just right of the midline. One day after the scan a thrombus located in the right posterior portion of the left atrium was found at the operation (Patient 9).

All tissue samples removed during the operation were weighed and counted for

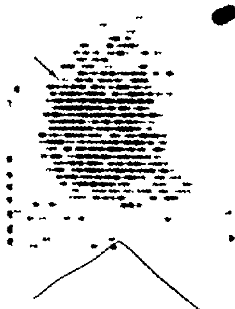


Fig. 3. Results of scan performed on Patient 9 (Tables I and II) 2 days after intravenous infusion of 131I antibody to human fibrinogen. The arrow points to an area of increased radioactivity corresponding to that of the posterior dorsal portion of the left atrium. At surgery the next day a thrombus was removed from this position.

131I activity in a well type scintillation counter along with a preoperative blood sample and an 131I injection standard. The percentage of the injected dose found in a weight of the sample equivalent to 1 per cent of the patient's body weight was calculated. A summary of such data is given in Table I. Ratios of 131I activity in each sample relative to blood are presented in Table II. Other studies have shown that the radioactivity in blood samples from individuals who have received 131I antifibrin antibodies is present in the plasma.[13] If clots are formed from plasma samples obtained 1 day to 2 weeks after infusion of the labeled preparation about 70 to 75 per cent of the radioactivity is found in the clot. This is the same percentage of clottability one gets if the 131I antifibrin antibody is mixed in vitro with human plasma and then clotted. It would thus appear that the isotope remains attached to the antibody for a long time and 131I determinations of whole blood will give an accurate estimate of the preparation originally injected and available for reaction with clotting fibrinogen. Since we are interested in comparing 131I in cardiac tissues and clots with that in blood on a unit weight basis, it seems that the whole blood values will give a more valid comparison of 131I destination than plasma counts and they are used in our data.

The radioactivity found in the various normal tissue samples is usually equal to or less than an equal volume of blood. Thus most of the 131I activity detected by the scanning procedure is due to blood borne radioactivity. In several cases (Patients 21 and 24) the 131I found in samples of mitral valve was substantially higher than in the blood indicating that the labeled antibody had concentrated on this tissue. Gross dissection of these valves indicated that the 131I antifibrin antibody had deposited on the calcified areas. This is shown in Tables I and II for those patients whose the higher 131I counts were on samples from calcified areas of mitral valve and whose lower values were from portions of the valve that were soft. The radioactivity in each of the thrombi found in the 4 patients was more than 14 times greater than an equal weight of blood. In 1 of these 4 patients, in whom the scan was falsel

Table I Results of scintillation scans and ^{131}I counts on surgical specimens

	Days between			% injected dose/Gm					
Patient No.	Isotope administration and scan	Scan and surgery	Scanning results	Blood	Atrial appendage	Mitral valve	Aortic valve	Tricuspid valve	Thrombus
1	2	1	−	4 5	8 4	5 4	—	—	—
2	2	1	−	4 8	0 4	1 8, 0 7	—	—	—
3	2	1	−	6 0	5 3	1 3	—	—	—
4	2	3	+	2 1	3 1	2 3	—	—	50 1
5	3	1	−	4 0	1 0	2 4, 0 8	—	—	—
6	2	1	−	Mitral commissurotomy					
7	3	1	−	2 8	—	1 2	—	—	—
8	3	1	−	3 7	1 0	1 0	—	—	—
9	2	1	+	3 8	2 1	1 2	—	—	23 6, 98.6
10	3	1	−	2 4	0 7	1 7	—	—	—
11	3	1	+	6 0	1 8	5 8		—	87 2, 132
12	3	1	−	4 5	7 9	1 9	—	—	—
13	4	2	−	2 1	1 1	0 4	0 5	0 4	—
14	5	1	−	5 4	3 2	4 7	—	—	—
15	2	1	−	5 2	0 5	1 1	—	—	—
16	4	1	−	2 5	—	2 0 0 9	4 7	—	—
17	2	1	−	Mitral commissurotomy					
18	2	1	−	4 2	0 5	—	0 6	—	—
19	4	1	−	2 3	0 4	0 7 1 0	0 8	—	—
20	2	1	−	4 9	1 7	1 5 1 9	1 3	—	—
21	3	1	−	3 7	3 7	0 7 10 4	−	—	—
22	2	1	−	3 5	0 5	0 9 5 2	−	—	—
23	2	1	−	Mitral commissurotomy					
24	3	1	+	4 1	1 7	1 7 13 8	−	—	—
25	2	1	−	4 3	—	—	—	—	4 3, 63 9
26	2	1	−	5 0	—	3 5	3 5	—	—
27	1	1	−	1 5	—	—	−	0 4	—
28†	2	1	−	—	—		−	—	—
29	1	1	−	4 2	—	0 7 4 8	−	—	—
30	2	1	−	6 5	8 6	—	—	—	—

*Normalized to per cent of patient body weight.
†Second study on Patient 8.

negative the thrombus was completely organized and most of it had an ^{131}I content that was in the same range as in the blood

That organized areas of thrombi will not concentrate ^{131}I antifibrin antibody can be seen from histological sections and their corresponding radioautographs shown in Fig 4 These are portions of the thrombus obtained from Patient 11 in Table I There are zones of very high ^{131}I activity that correspond to portions of thrombus that show some vascularity and cellular detail (Fig 4 *A* and *a*) Other sections show little if any cellular detail and vascularity (Fig 4 *B*) In these we do not find much ^{131}I activity (Fig 4 *b*) Comparable findings were obtained in sections and radioautographs from Patients 4 and 5 Table I Thus thrombi composed almost completely of organized material will not have a very high concentration of radioactivity and will not be easily detected by scanning procedures.

Discussion

In the 4 patients in whom atrial thrombi were found at operation ^{131}I determinations on these lesions indicated a very high concentration of radioactivity compared with blood and other cardiac tissues. The

Table II Ratios of ¹³¹I activity in various tissues

Patient No.	Atrial appendage blood	Mitral valve blood	Other tissue blood	Thrombus blood
1	1 8	1 2	—	—
2	0 1	0 4 0 2	—	—
3	1 0	0 2	—	—
4	1 4	1 1	—	3 4
5	0 2	0 6 0 2	—	—
6	—	—	—	—
7	—	0 4	—	
8	0 3	0 3	—	—
9	0 6	0 3	—	6 2 25 9
10	0 3	0 7	—	—
11	0 3	1 0	—	14 2 22 0
12	1 8	0 4		—
13	0 3	0 2	0 2 0 2	
14	0 6	0 9	—	—
15	0 1	0 2	—	
16	—	0 8 0 4	1 9	
17	—	—	—	—
18	0 1	—	0 1	
19	0 2	0 3 0 4	—	—
20	0 4	0 3 0 4	0 3	—
21	1 0	0 2 2 8	—	—
22	0 1	0 3 1 5	—	—
23	—	—	—	—
24	0 4	0 4 3 4	—	—
25	—	—	—	1 0 14 9
26	—	0 7	0 7	—
27		—	0 4	—
28	—	—	—	—
29	—	0 2 1 1	—	—
30	1 3	—	—	—

of isotope in the thrombi to normal tissue was great enough to enable it to be suspected in 3 of 4 cases by scintillation scanning techniques. Large variations in the percentage of the injected dose present per gram of thrombi were found and these are very obvious in the radioautographs where relatively hot and cold spots were seen Two factors may be responsible for this phenomenon One is the extent of organization of the clot. Well-organized clots with the resultant loss of vascularity do not have any appreciable localization of radioactivity This is probably due to the lack of ability of the fibrinogen ¹³¹I antifibrin complex to penetrate this avascular mass. It is primarily in the areas where recanalization has occurred that there are zones of intense radioactivity [1]

Another factor is that deposition of the ¹³¹I antifibrin antibody depends on the extent of the acute inflammatory response. There appears to be close correlation between areas of polymorphonuclear infiltration and zones of high radioactivity It would seem as though a portion of the ¹³¹I antifibrin antibody is being concentrated in the lesion as a result of an acute inflammatory response during the initial phases of organization Similar events were noted in studies on the localization of ¹³¹I antifibrin antibody in deep venous thrombi.[1]

It does not appear likely that the ¹³¹I antibody to human fibrinogen combines with fibrin already deposited in lesions, such as thrombi Rather it would seem as though the injected labeled antifibrin antibody complexes with circulating fibrinogen which is present in excess, and as this is converted to fibrin it brings along with it the attached antibody In our studies there are several possibilities to account for the deposition of fibrinogen as fibrin along with ¹³¹I labeled antibody It can occur as a result of the conversion of fibrinogen to fibrin in an area of acute inflammation on the thrombus. It can also take place as the result of formation of new thrombus or as a consequence of a dynamic equilibrium between lysing fibrin (due to plasmin activation) and new fibrin formation

Studies with ¹³¹I fibrinogen indicate that this preparation does not have the property of concentrating to any great extent in preformed thrombi.[7] This may be due to its degradation by plasmin after it has been converted to fibrin with resultant removal of the isotope. ¹³¹I antibodies to human fibrinogen do concentrate better possibly because of its nonreactivity with plasmin. It seems possible that a molecule of ¹³¹I labeled antifibrin antibody after loss of its antigen i.e. fibrin simply attaches itself to another fibrin molecule in the immediate vicinity This leads to a maintenance of radioactivity in the site of its original concentration when the antifibrin antibody is the carrier of the radioisotope. When ¹³¹I fibrinogen is used on the other hand as the fibrin is catabolized the radioisotope is solubilized

The ability to detect by scintillation scanning an intra-atrial thrombus after

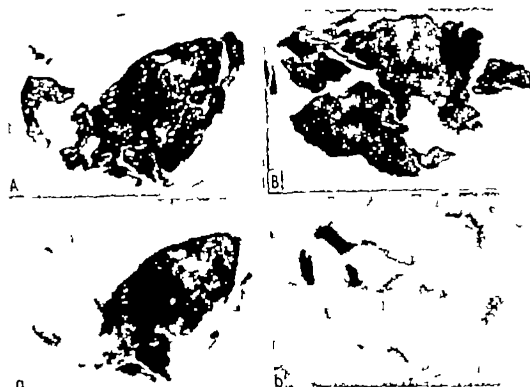


Fig. 4 Histologic sections and corresponding radioautographs made from thrombus removed from Patient 11 (Table I). Highest levels of radioactivity correspond with portions of the section that retain cellular detail.

administration of [131]I antibody to human fibrinogen depends on the relative concentration of isotope in the lesion to that in the circulation. From the [131]I counts made on samples of thrombus, normal heart tissue and blood there is a substantial concentration of the labeled preparation in the thrombus compared to an equal weight of blood. However since the thrombus is located in a blood pool, the unit ratio of [131]I is somewhat decreased since the focusing collimator on the scanner detects radioactivity efficiently to a depth of at least 5 cm. Thus as the moving probe passes over the ventricle the blood volume of this heart chamber reduces somewhat the absolute difference in [131]I concentration between the thrombus and normal blood and makes it more difficult to differentiate between circulating radioactivity and radioactivity concentrated in a thrombus. This "hot" thrombus becomes even more obscure when the atrium is enlarged. Thus the [131]I ratios in thrombus to blood found on a unit weight basis can be diminished considerably when the scanning procedure is used and may lead to misinterpretation of the scan.

[131]I antifibrin antibody concentrated in thrombi can be visualized more easily as there is a substantial increase in the ratio of the radioactivity in the thrombus to that in the blood. This can be accomplished by increasing the interval between administration of the radioactive material and scan. As the blood-borne [131]I preparation is catabolized the radioactivity in the thrombus decreases at a slower rate. Thus the relative [131]I content in the thrombus is steadily increasing. However because of the physical decay of the [131]I one may have to increase the dose administered in order to get statistically significant counts if there is too long an interval between administration of the labeled preparation and the scan.

The use of [131]I rabbit antibody to human fibrinogen as a diagnostic preparation has led to no clinical reactions in over 300 patients who have been studied.[3,4,6] Many

have had blood samples as well as scanning procedures done as long as 2 to 3 weeks after intravenous administration of this labeled protein with no evidence of immune reactions or rapid elimination The biological half life remains constant at 5 to 7 days This may be related to the very small amount of foreign protein actually given Since after ^{131}I labeling there are about 100 mc attached to 4 mg of antibody most patients are infused with less than 0 1 mg of rabbit antibody to human fibrinogen This seems not to evoke specific antibody production even after a second administration of the diagnostic preparation A few patients after negative skin tests have shown very rapid disappearance of the ^{131}I antibody Careful questioning of these individuals showed that they had had extensive exposure to rabbits i e as a hunter or laboratory technician There was no clinical evidence that immune elimination was going on presumably the quantity of reactants was too small to evoke any systemic manifestations.

A more satisfactory technique that may eventually permit a smaller amount of ^{131}I to be used for this procedure is to reduce a major portion of the circulating radioactivity by an immunologic procedure. Since the ^{131}I is actually attached to rabbit gamma globulin it is possible to remove over 75 per cent of the blood borne radioactivity by administration of preparations containing goat antibodies reactive to rabbit gamma globulin This has already been done in experimental animals and it has been found that a very rapid removal of the circulating ^{131}I rabbit antibody to fibrinogen can be obtained with very little reduction of the portion of the labeled preparation that is concentrated in tumors.[8] Initial studies on human subjects indicate that this is a safe procedure.[9, 10] In one study the in vivo reaction involved as much as 1 000 times more protein than our series and there were no immediate clinical consequences. Studies in experimental animals[7, 8] indicate that the ^{131}I labeled rabbit antifibrin antibody even after its in vivo reaction with goat antiserum to rabbit gamma globulin does not accumulate in the kidney In the latter case, the ^{131}I accumulates immediately in the liver and to a lesser degree in the spleen About 6 to 12 hours later nonprotein bound ^{131}I appears in the blood and this is rapidly excreted. There is no evidence of any deposition of radioactivity either before or after immunologic removal in the kidney

It is hoped that by utilization of immunologic removal of the major portion of the radioactivity that is not bound to the thrombus more reliable scans will be obtained By decreasing the ^{131}I antibody that is present in the circulation the ratio of ^{131}I in the thrombus to that in the blood will be appreciably increased and this would lead to easier detection of concentrations of ^{131}I in thrombi as well as of smaller thrombi With the introduction of the second step it is hoped that detection of thrombi in blood pools can become a more routine diagnostic procedure that is as accurate as, but less traumatic than the present techniques involving cardiac catheterization and angiocardiography

Summary

Scintillation scanning to detect atrial thrombi after intravenous administration of ^{131}I labeled antibodies to human fibrinogen was performed on 30 patients who had mitral valve surgery under cardiopulmonary bypass. Twenty-six patients had negative scans and at operation no thrombus was found in 25 Of the 4 patients with positive scans 3 had left atrial thrombi at surgery and 1 had a highly calcified valve ^{131}I determinations of blood, surgically removed cardiac tissue and thrombi demonstrated that the thrombi could have as much as 25 times more ^{131}I than that in an equivalent amount of blood Little ^{131}I accumulation was found in organized avascular portions of the thrombus or atrial appendage, mitral valve and tricuspid valve.

Because of the high concentration of ^{131}I in the thrombus compared to that in the cardiac tissue and blood this procedure seems promising as a means of detecting atrial thrombi with little discomfort to the patient. It is suggested that the use of an antiserum to rabbit gamma globulin to remove immunologically the major portion of the blood borne ^{131}I rabbit antiserum to human fibrinogen may appreciably increase the ratio of thrombus to blood and this would decrease the possibility of false-

negative scans and increase the resolution of positive scans.

We are indebted to Dr. William F. Bale for his advice during this study and his assistance during the iodination of the antibody.

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Blind study on the action of digitoxin on elderly women

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Easily demonstrated in atrial fibrillation, the cardiac action of digitalis glycosides is so much less conspicuous in patients with normal rhythm that some distinguished clinicians have doubted that there was any cardiac effect at all in such cases.[1,2] In contrast, when tested in animal preparations the cardiac action of digitalis is easily demonstrated during normal rhythm.

Many workers have hoped that estimations of cardiac output would resolve the discrepancy by providing evidence of cardiac stimulation of a degree not recognizable by clinical observation. Selzer and Kelly[3] have reviewed the recent literature and Starr and associates[4] the older. The results are scattered; when digitalis glycosides are given to healthy persons or to cardiac patients in normal rhythm, no consistent effect on cardiac output has been demonstrated.

Other measurements may provide a more sensitive method. Thirty years ago Starr and associates[4] found that changes in the heart work-size ratio provided evidence of stimulation by digitalis when cardiac output did not. Recently, working on healthy persons and patients with normal rhythms, Weissler and co-workers[5] concluded that the cardiac action of digitalis glycosides manifested itself in a slight shortening of ejection duration without altering stroke volume. This work suggests that stimulation would be better detected by measuring ejection velocity, the first time derivative of stroke volume, than by measurements of stroke volume itself.

Measurements related to the second time derivative, acceleration, might be still more sensitive. In animal experiments, Noble and colleagues[6] found that, by a suitable dose of epinephrine, ejection acceleration could be increased by 50 per cent although stroke volume was unaltered. Braunwald and associates,[7] measuring cardiac forces (force = mass × acceleration) by a strain gauge arch applied directly to abnormal hearts exposed at operation with the patient on cardiopulmonary bypass, consistently demonstrated cardiac stimulation during the action of rapidly acting digitalis

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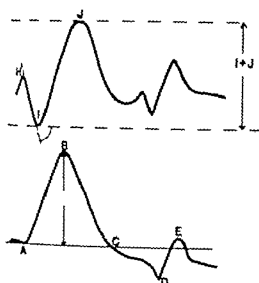


Fig. 1 Measurements made on the records studied in the force BCG (above) the vertical IJ amplitude, indicated on the right, and HI slope, the tangent of the angle of the HI segment with a horizontal line, were measured and converted to the values given by means of the calibration.

Measurements made on the carotid pulse derivative (PD below) included the AC duration, and the vertical distance from the base line to the "record" peak at B, which represents the maximum rate of blood pressure rise in each beat. The calibration was based on the pulse pressure, determined by the auscultatory method, and a measurement of the maximum slope of the conventional pulse wave front (for details see Starr and Ogawa[11]). Since the PD cannot be easily calibrated before the test, the calibration of the records reproduced often differs and comparison of PD amplitude by inspection must take this into account.

glycosides. Though the clinical situations were so altogether different that comparison is hazardous, this interesting finding contrasts with the many failures to demonstrate cardiac stimulation after such drugs by measuring cardiac output in patients and healthy persons in normal rhythm.

The large experience with the force ballistocardiogram (BCG) supports the same belief. Cardiac stimulation both by sympathomimetic drugs and by physiological agents such as exercise causes conspicuous increases in the forces recorded from men and animals. Given to patients with atrial fibrillation digitalis glycosides are often followed by striking improvement in the form and amplitude of the force record and this is also true when such drugs are given to certain sick cardiac patients with hearts in normal rhythm.[3] Fig. 1 gives an example of what is a common experience in hospital wards.

But we were not happy with evidence of the type shown in Fig. 1 and the criticism applies to the work of many others as well as to our own. While the cardiac stimulation may well be due to digitalis, who can say with confidence that the sedatives the patient received, the special diet, the bed rest in a comfortable position, the reassurance, the diuretics, and the natural processes of recovery may not have contributed to the result?

A much more decisive test of digitalis action in the clinic is to withdraw the drug after maximum clinical improvement has been secured; if cardiac function then deteriorates, the conclusion that digitalis was the cause of the original improvement is very hard to avoid. But, requiring close supervision and a long stay on the wards, only in a few cases with atrial fibrillation has such a study been accomplished in this hospital. In these the deterioration of cardiac forces after withdrawal of digitalis was as conspicuous as the original improvement. We had long been awaiting an opportunity to subject patients with normal rhythm to the same experiment.

An interesting experiment of this kind was made recently by Priddle and Rose who had available 110 elderly patients receiving digitalis, diuretics, and a low sodium diet in a geriatrics clinic. Extremely cautious, they considered it safe to withdraw the digitalis in only 13 of these; surely many doctors would have shared their fears. In 5 of these patients breathlessness was judged to be increased after withdrawal and digitalis administration was resumed. The remaining 8 were judged to be as well off without it as they had been before.

A number of factors had combined to interest us also in a study of digitalis action in the aged. "I would rather take milk from a baby than digitalis from the arteriosclerotic heart" was a favorite aphorism of "Big Bill" Smith as he strode the wards of the Massachusetts General Hospital 50 years ago, followed respectfully by senior author Dr. William D. Stroud.

counseling his elderly patients used to liken digitalis to insulin in order to accustom them to the idea that they must continue to take it indefinitely But one of Stroud's elderly patients having an excellent exercise tolerance despite auricular fibrillation decided that she was much too well to take any drugs and stopped taking digitalis. This action against advice had not the slightest effect on her well being that the senior author a close relative could detect she went without the drug for many years and was very active up to a week of her death from cardiac infarction at the age of 88

Opportunity came because Dr Luchi was in charge of the health of a group of elderly women residing in a retirement home close to the University Hospital and so we were able to design an experiment on digitalis action which seemed to us, far superior to any that had been performed before. Under the plan envisioned we could (1) work on patients in a steady state with regard to their health and so avoid the spontaneous changes in cardiac action which might accompany the variations of acute illness so often found in ward patients (2) withdraw digitalis glycosides from our subjects, some of whom had been on them for years, under such close observation that should it lead to deterioration of their health this would be immediately detected and appropriate measures taken (3) use the ordinary clinical methods to the full in judging the drug's action but safeguard ourselves against unconscious bias by having both patients and observers in ignorance of whether the drug was being given or not (4) use methods of study which did not disturb the patients in any way so that the confusion introduced by emotional factors either would be absent or at a minimum in our results (5) secure records of the forces of the heart and circulation and of the derivative of the pulse in order to have very sensitive methods of detecting cardiac stimulation should it occur (6) make repeated trials of giving and withdrawing digitalis in the same subject to test for the consistency of the effects (7) study the action of digitalis glycosides given over long periods of time in the same dosage and manner as is standard practice (8) study digitalis action in elderly patients who had heart disease as judged by conventional criteria as well as in those who had not (9) determine the inherent variability of the aspects of cardiac function measured both when digitalis was being given daily and when it was not being given at all to permit comparison of the magnitudes of spontaneous changes with those found after the drug had been started or withdrawn There seemed little doubt that a statistical analysis of such data would provide better evidence of the presence or absence of digitalis effects in elderly subjects than is contained in any other study of which we are aware.

But in one respect we were disappointed. Although almost 200 elderly women came under our observation in the 5 years of the study we found only one with auricular fibrillation and she died before digitalis had been withdrawn Perhaps it is unusual for those with this disability to live as long as our other subjects. So this study is concerned with digitalis action in persons in normal sinus rhythm.

Subjects

The 12 elderly women studied resided in a retirement home located several blocks from the University Hospital. Their ages ranged from 73 to 94 years, and averaged 85 years. For identification they have been given numbers in order of age No. 1 (age 73) to No 12 (age 94) A complete clinical study of each subject was made. None was, or recently had been in an acute difficulty such as congestive failure or cardiac infarction

Our subjects can be divided into two groups Patients Nos. 1 2 4 6 8 and 11 were believed to have heart disease because they had one or more of the following a history of congestive failure, typical angina pectoris, or an enlarged heart by x ray Similar evidence of heart disease was absent in the others although many had definite evidence of peripheral arteriosclerosis. All were in normal sinus rhythm but Patient No 2 who died of a cerebrovascular accident before we could get a test of digitalis effects. Patient No. 6 died of myocardial infarction during the study and Patient No 11 died presumably of dissecting aneurysm soon after the study

was finished. Table A* gives additional clinical information.

The BCG abnormalities found in these elderly subjects have been the subject of another report,[9] except for some tests in the youngest of our subjects, age 73, all the BCG's recorded were markedly abnormal in contour and small in amplitude. As is almost always the case in the elderly their hearts no longer contracted with the vigor of youth and in most the contraction was to some degree incoordinate.

Despite such disabilities all our patients were ambulatory and considered themselves in reasonably good health at the time we tested them. They gladly volunteered for the study.

The study

Fearing that the withdrawal of digitalis glycosides from patients who had been taking them for many years might lead to a deterioration of health, Dr. Luchi supervised the administration and withdrawal of digitoxin himself for the first year of the study, while Dr. Starr and the patients were "blind." 23 tests on 9 subjects were made this way. By that time it was evident that untoward effects from digitoxin withdrawal were not to be feared. So Dr. Luchi also went "blind." Twenty-five tests on 3 subjects were performed this way.

Through the kindness of Dr. Ch u of the Eli Lilly Company, placebo tablets identical in appearance with tablets of 0.1 mg. of digitoxin were secured; the active drug and placebo were designated A and B, the code being known to neither author. Which was given first was selected by lot. In all chronic experiments, digitalis periods of a month or more duration alternated with control periods of similar length. Administration of the drug was started by giving 1.2 mg. of digitoxin by mouth in the first 2 days and continued by 0.1 mg. P.O. daily thereafter. During control periods the subjects received no digitoxin, but those with a history of congestive failure continued to receive their usual dose of diuretics.

We made a few experiments designed to detect the acute effect of larger doses of digitoxin. Four subjects, who had been off digitalis for a month or more, were studied on the day before and on the first or second day after receiving doses of 0.6 to 0.8 mg. of digitoxin by mouth.

To estimate the effects of the medication Dr. Luchi saw the subjects several times a week throughout the study and attempted to decide whether they were receiving digitoxin or not by the usual clinical criteria.

The battery of tests conducted by Dr. Starr was performed before and two weeks or longer after the beginning of each period and at intervals thereafter, the patients coming to the University Hospital by taxi. In these tests every effort was made to avoid the emotional tensions inherent in the operating room atmosphere so often found when cardiac studies are made by modern methods. Our patients came to the laboratory in groups and watched each other being tested. Each subject rested for 15 minutes before records of the ULF force BCG, the carotid pulse derivative,[11] and the blood pressure were taken. After all subjects had been tested we served tea or candy which contributed no little to making the occasion enjoyable; indeed it was anticipated with pleasure by our old ladies.

All records were read the day they were taken. The measurements made are indicated in Fig. 1. After the experiments had been completed, but before the code had been broken, the BCG's of each subject were arranged in order and the adjacent tests directly compared with one another for evidence of improvement or deterioration of cardiac function.

Results and discussion

Two preliminary reports have been made.[11,12]

After the code had been broken it was found that we had 17 pairs of observations made before and after digitoxin had been started, 8 pairs made before and af

*Table A, giving detailed clinical descriptions of our subjects, and Table B, which contains pages of raw data which form the basis of the study have been filed with the National Auxiliary Publications Service of the American Society for Information Science (ASIS-NAPS), 909 3rd Ave., New York, N. Y. 10022. These tables have been deposited as Document Number NAPS-[illegible]. Copies can be obtained from that service by remitting with the order $[illegible] for photoprints or $[illegible] for 35 mm. microfilm. Make checks or money orders payable to ASIS-NAPS.

*Table I Examples of the data secured**

Parameters	August 27 on digitalis	October 4 off digitalis	October 24 on digitalis
BCG findings			
HI slope (tangent)†	1 4	3 1	1 9
IJ amplitude (Gm)	45	57	45
Degree of abnormality of contour estimated by inspection	++++	+++	++++
Carotid pulse findings			
BP (mm Hg)	180/80	170/80	210/100
Pulse pressure (mm. Hg)	100	90	110
Average duration of rising pressure (sec.)	0 22	0 24	0 19
Average slope of rising pressure— quickness of the pulse (mm Hg/sec.)	450	375	580
Maximum slope of rising pressure (mm. Hg/sec.)	1 187	1 072	1 431
Heart rate per minute	70	68	65

*Patient No. 4 had been taking 0.1 mg. of digitoxin daily for many years. On September 19 this was stopped, and on October 13 she was digitalized (1.2 mg. of digitoxin P.O.) and placed on the same maintenance dose as before.

†The calibration was: vertical, 1 mm. = 18.7 Gm. of force; horizontal, 1 mm. = 0.04 sec. Therefore, in absolute units, a tangent of 1.4 equals 661 (10⁹) dynes per second.

had been stopped and 17 controls, i.e., tests similar in every way except that the drug had been neither started nor stopped between the pair.

Typical data obtained in one subject are given in Table I. Similar data on the other 11 subjects are given in Table B which, too long for publication here, can be secured from the National Auxiliary Publications Service by anyone interested.

Since in any statistical study there is always danger that data from the nonreactors may dilute that of the reactors below the level of significance, the results secured on individuals will be considered first.

Results on individuals. The patients queried by Dr. Luchi in regard to their well being and exercise tolerance were altogether unable to tell whether they were receiving digitoxin or not.

By the ordinary clinical observations Dr. Luchi detected no changes which would permit him to decide whether his patients were receiving digitoxin or not.

Of the more objective tests, the form of the BCG was the most interesting, especially since the small changes were identified without knowledge of their relation to the drug's administration. Since the BCGs in every patient but one were always highly abnormal, we had every reason to expect that cardiac stimulation would be easily recognized by improvement in form and amplitude. But it must be emphasized that the differences of BCG form recorded in Table II, identified by direct comparison of adjacent records, were almost always much smaller than those commonly used to assign magnitude of BCG abnormality in clinical work. Fig. 2 gives typical examples of the small differences encountered in this study.

The changes in quantitative measurements such as pulse rate, blood pressure, pulse pressure, rate of pressure rise, and the forces of the circulation which followed the introduction or withdrawal of digitoxin were similar to the spontaneous changes encountered in the same subjects.

Nevertheless, there are certain items of interest. Patient No. 1, a case of hypertensive cardiac disease, and our youngest subject, after receiving digitoxin for the first time had a cardiac stimulation equal to that sometimes seen on the wards, the

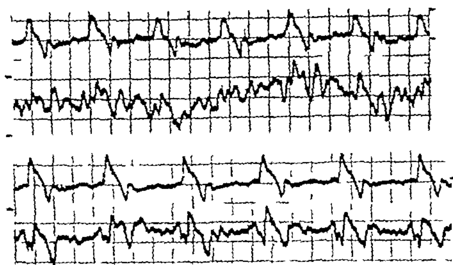


Fig. 2. Digitalis action ... young patient in normal sinus rhythm. Carotid pulse derivative over ULF force BCG on Patient T. H., age 42, who has diabetes and treated hypertension. The upper pair of records were taken in May 11, 1967, when she had slight edema of the feet, although she could lie flat with comfort. Blood pressure was 120/100 mm. Hg. She had received no digitalis for many months. Note that the initial jerk is hard to locate and that the other distortions of the BCG are so great that it would be difficult to identify systole without the simultaneous pulse record.

After the first test the patient received 0.2 mm. of digitoxin 5 times in 24 hours and 0.1 mg. daily thereafter. At the second test a week later blood pressure was 123/94 mm. Hg. Note that the systolic complexes in the BCG are now clearly seen, the initial jerk (HI in Fig. 1) has greatly increased in prominence and the average overall amplitude (I J, Fig. 1) is greater than before digitalis. Much more normal than the first record, this record cannot be passed as altogether normal in form, for prominent notches on the HI segment and in the smaller J waves remain. The PD has greatly increased in amplitude and the take off angle (A (Fig. 1) is much sharper than before digitalis. Pulse pressure has also increased notably. The patient lost 7 lb. of weight between the two tests.

Calibration of the pulse derivative (right) = 500 mm. Hg per second between marks. Calibration of BCG (left) = 280 Gm. of force.

only instance in which a conspicuous stimulation occurred after digitoxin in this study. Fig. 2 shows the records secured. After withdrawing it repeatedly, digitoxin was started 3 times more in this subject, and evidence of improvement was much less marked in 2 experiments and altogether absent in another. Two controls showed that the inherent variability in this subject was as great as that encountered in 3 of the 4 digitoxin tests and the striking effect secured on the first test was never repeated.

Before our study six of our patients had been receiving digitoxin daily for so long that the beginning was hard to date exactly. Patients 1, 7, 8, and 11 had been on it for 6 years or longer. Patient 4 for many years. All were withdrawn without developing any untoward symptoms or signs that we could detect and they were all unconscious that anything had been changed.

Obviously, in no subject did we secure unequivocal evidence that digitoxin consistently stimulated the heart.

Study of cardiac and noncardiac groups. The clinical data enabled Dr. Luchi to divide our subjects into cardiac and noncardiac groups. These were equal in size and Table II was arranged to display any differences that might exist between the BCG findings of the two groups. Inspection shows at once that the differences are not conspicuous. Among the cardiac patients the BCG behaved as if digitoxin had slightly stimulated the heart in 6 out of 15 tests, in the noncardiac patients in 2 of 10 tests; chi square is not significant for either. Nor could we find significant differences in the other data we had accumulated.

Study of the group as a whole. Since the

Table II. Change in BCG form, estimated by inspection with the reader "blind," when digitalis was started, stopped, continued unchanged, or not administered

Subject no.	Experiments in which digitalis was						Controls in which digitalis was					
	Started			Stopped			Continued			Withheld		
	Instances in which BCG was judged to be			Instances in which BCG was			Instances in which BCG was			Instances in which BCG was		
	Better	Worse	Not changed	Better	Worse	Not changed	Better	Worse	Not changed	Better	Worse	Not changed
Cardiac												
1	2		1	1	1		1	1				
2								1	1			
4			1			1						
6	1		1					1				
8	1		2		1			1	3			1
11		1		1							1	
Total	4	1	5	2	2	1	1	4	4	0	1	1
Noncardiac												
3	1						1	1				
5			2						1			
7						1						
9			2			2	1	1				1
10			1									
12	1								1			
Total	2	0	5	0	0	3	2	2	2	0	0	1
Grand total	6	1	10	2	2	4	3	6	6	0	1	2

form and amplitude of the BCG's of our old ladies differed so markedly from those of healthy young adults, they can all be thought of as having abnormal hearts, and it is permissible to combine them into one group.

For statistical analysis the data were first arranged in pairs. Thus, each measurement made on Patient No. 4 (Table II) on August 27, when the patient was on digitoxin, was paired with the corresponding measurement made on October 4 when she had been off the drug for three weeks, and the latter value was subtracted from the former, resulting in a series of differences (H-I slope difference −1.7, I-J amplitude difference −12, pulse pressure difference 10, etc.) which might be due to the stopping of the drug. By pairing the items in the last two columns similar data on changes initiated by digitalis action were sought. Data secured on the other subjects were handled similarly.

One comment is necessary. In the example cited in Table II the same control was used for two drug tests, but in most other subjects this double use of control values was not necessary. If it was avoided the number of pairs available for the analysis of digitalis action is reduced, but the conclusions are unaltered. Only consecutive tests were paired.

The data displayed in Table III can be analyzed in several ways, the most important of which is to ask whether the mean differences found in each column are significantly different from zero. Inspection shows that all these means are smaller

Table III

Parameters	*Digitoxin experiments*						*Controls†*		
	Chronic experiments			*Acute experiments*			*Chronic experiments*		
	no.	mean‡	sigma	no.	mean‡	sigma	n	mean§	sigma
BCG findings (flow)									
H I slope (tangent)	21	0.26	1.6	4	−0.17	1.3	17	−0.04	0.97
I J amplitude (Gm.)	21	10	32	4	9	5	17	0.04	1.31
Pulse findings (pressure)									
Systolic B.P. (mm. Hg)	20	6	21	4	6	12	17	2	16
Diastolic B.P. (mm. Hg)	20	−1	16	4	13	13	17	8	14
Pulse pressure (mm. Hg)	20	7	18	4	−9	12	17	−4	16
Average duration of rising pressure (sec.)	20	−0.02	0.03	4	−0.06	0.04	17	0	0.04
Average slope of rising pressure, quickness of the pulse (mm. Hg/sec.)	19	84	117	4	72	118	17	−16	208
Maximum slope of rising pressure (mm. Hg/sec.)	17	−145	635	4	−550	724	17	−149	473
Heart rate	21	2	10.2	4	−3	5	17	−2	9

*Average effect of the drug on elderly women. Differences between pairs of measurements made before and during, or during and after digitalis action.

†Average differences between two measurements made at intervals of week or more during digitalis action, or in its absence.

‡Minus sign indicates that the measurements made during digitalis action were less than the control.

§Minus sign indicates that the measurements made at the first test were less than those of the second.

than their standard deviations. So t is less than one for each item and not one of the means is significantly different from zero.

In Table III one can also compare the mean differences shown in column 1 with the corresponding items in column 3: the differences recorded in the first column could be due to the presence and absence of digitalis action; those recorded in the last column could not. As would be expected from the experimental design none of the means in the last column of Table III is significantly different from zero. The standard deviations shown in this column define the inherent instability of our subjects which is small for the items we measured. This is gratifying, for it shows that we were successful in running our experiments without objectionable emotional content. The means and standard deviations recorded in columns 1 and 3 are surprisingly similar; needless to say in none of the items measured are the differences between them significant.

In the analysis just described each pair was given equal value with every other despite the fact that more tests were secured in some subjects than in others. If one corrects for this, the means and standard deviations are so very close to those recorded in Table III that we have not recorded them here.

The results recorded in Table III also demonstrate that the means secured in the *four* acute digitalis experiments are very similar to those of the chronic experiments, and none of them is significantly different from zero. So by an analysis of this type we were still unable to detect any evidence of cardiac stimulation by digitalis in either acute or chronic experiments in our elderly subjects.

Indeed, we found no significant differences at all.

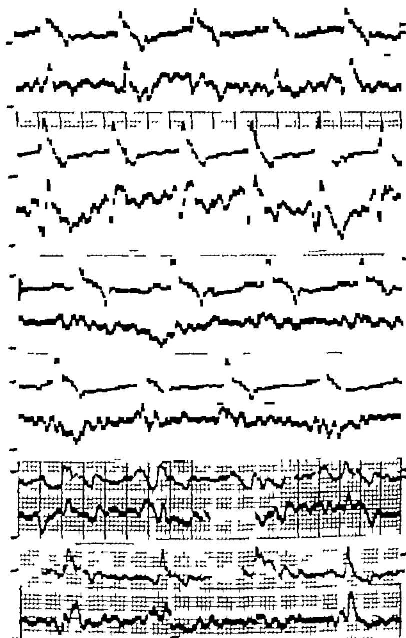


Fig. 3. Records secured in elderly subjects during and in the absence of digitalis action. Carotid pulse derivative and ULF force BCG before and during the administration of digitoxin. Calibration of PD = 500 mm. Hg/sec. (right) of BCG 280 Gm. (left).

Top pair: Records of Patient No. 1, age 73, before (December 1) and during (January 15) the administration of 0.1 mg. of digitoxin daily started with one large dose after the test on December 1. Note the markedly improved HI downstroke, the increased IJ amplitude and improved form in the second record. The apparently increased amplitude of the PD in the second record is due to differences in calibration.

Middle pair: Records of Patient No. 3, age 79, before (April 22) and during (May 5) the administration of 0.1 mg. of digitoxin daily started on April 23 after the patient had been given 1.2 mg.

In the control record, BCG amplitude is greatly reduced. The jerk is so small that it is difficult to locate, and the contour so abnormal that it is hard to identify the waves with confidence: an extremely abnormal BCG. During the drug's action there is little change. Perhaps BCG amplitude is a little larger and the jerk more prominent, but contour remains extremely abnormal. The PD is essentially unchanged.

Lower pair: Records of Patient No. 6, age 86, before (April 22) and during (May 5) the administration of 0.1 mg. of digitoxin daily started on April 23 when she received a total of 1.2 mg. Note great distortion of both control records and absence of the normal jerk in the BCG. In the second pair there is little if any change. The apparent increase in PD amplitude is due to a difference in calibration.

Did the patients receive active digitoxin? Confronted with a completely negative result when we had expected the reverse this question immediately presented itself The blind study has many advantages and some alarming disadvantages it removes the blind investigators from close contact with what actually took place. If by some mischance both bottles had contained the placebo the authors might not have been aware of it and thus was a possible interpretation of our results. We plainly needed a demonstration that the patients had received active digitoxin

We discussed our problem with Dr George B Koelle Professor of Pharmacology who kindly offered to conduct a simple check of the biological activity of the tablets by means of a modification of the one hour frog test which was employed in the U.S.P XI biological assay for digitalis preparation. Five frogs were injected via the abdominal lymph sac with varying amounts of an alcoholic extract of the tablets, and one hour later they were pithed and the hearts were examined Only at excessively high doses was there any suggestion of the characteristic systolic arrest that would be expected from an active preparation under conditions of a well-controlled assay which it should be emphasized this preliminary study was not. Dr Koelle consoled us by pointing out that the irregularity of the results secured in frogs by this method had eventually led to its abandonment. However since two sets of results now suggested that there might be an inactive digitoxin preparation on the market, it seemed wise to turn the matter over to the Food and Drug Administration for adjudication. We are indebted to Deputy Director William J Conway Jr for permission to publish the results of their tests. The sample from the tablets believed to contain the active drug contained by chemical test 96 per cent of the stated amount of digitoxin Four lots of the same material obtained from the manufacturer tested chemically contained 96 98 97 and 99 per cent of the digitoxin expected Two samples were examined by a biological assay similar to that of U.S.P XIII except that pigeons were used instead of cats as test animals and that a standard developed in the Food and Drug Administration laboratory was used in place of the U.S.P standard One sample assayed biologically at almost 114 per cent of potency the other assay was not completed but the sample was at the upper limit of satisfactory potency

Obviously despite the uncertainty caused by the negative finding in frogs, the digitoxin we used met all official standards. So we must search elsewhere for an explanation of our very negative results.

Can the elderly heart respond to stimulation? The negative results after digitalis raise the question whether these old hearts may not have been working so near the limit of their capacity that further stimulation was impossible. This could be answered by testing after exercise, and at the end of the study 7 of the 12 subjects given digitalis were still available.

The technique was very similar to that of Makinson. BCG and blood pressure were taken after 15 minutes of rest in the horizontal position and then the subjects arose and made 10 trips up and down 2 steps, each step 9 inches in height. They chose the speed themselves and most took about 2½ minutes to complete the trips. Then they lay down on the BCG immediately and records were taken at frequent intervals for 10 minutes.

In Subjects Nos. 1 7 9 10 and 11 marked cardiac stimulation was demonstrated after the exercise by increased BCG amplitude and slope while the form of the record if abnormal before exercise became more normal after it Fig 4 gives an example On the average, the recorded forces doubled, while heart rate and blood pressure increased a little after exercise in most cases. These manifestations of cardiac stimulation gradually diminished and in most subjects, had disappeared in 10 minutes.

In two subjects, Nos. 3 and 8 the test done three years after the digitalis study was less satisfactory because the first record made after exercise was so distorted by artifacts from the violent respiratory movements that the cardiac complexes could not be identified. However the subjects dyspnea slowly diminished as they rested and within a few minutes cardiac complexes reappeared Although the hearts of our other subjects were still

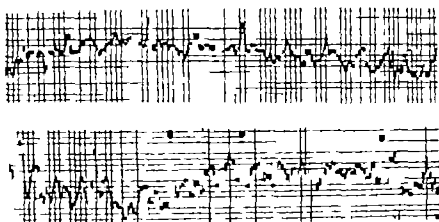


Fig. 4. Effect of exercise on an elderly heart (Subject No. 9, age 89). *Upper*, ULF force BCG before exercise, blood pressure 130/80 mm. Hg. *Lower*, Same record 2 minutes after walking over 2 steps 10 times, blood pressure, 162/82 mm. Hg. Note great increase in BCG amplitude and improvement in form; the jerk almost absent before exercise is strong after it. BCG calibration = 280 Gm. This subject's heart, strongly stimulated by exercise, was not stimulated by digitoxin.

stimulated at that time the force records of these two subjects were smaller and more abnormal than before exercise. In Subject No. 8, blood pressure rose considerably but in No. 3 it fell after exercise.

Thus the ability of the heart to beat more vigorously was easily demonstrated in 5 of the subjects who had failed to respond to digitalis, so we must conclude that the failure of that drug to stimulate their hearts was not due to the incapacity of their hearts to respond. But in 2 of our cases cardiac incapacity is a possible explanation for our negative results.

In addition, the results secured in these exercise experiments demonstrate conclusively that changes in the BCG permitted the ready identification of cardiac stimulation in our old subjects when it occurred. Evidence that this is true for younger subjects, when the heart is stimulated by many agents both in animals and in man, has already been presented by many authors.[4]

Summary

In 11 elderly women, all in normal rhythm and some with manifest heart disease, digitoxin and control periods, each of about a month's duration, were alternated. In 6 patients who had been taking digitoxin daily for many years the drug was withdrawn. A few acute experiments were made.

Both the patients and the observers were blind; the latter attempted to identify digitoxin action both by the ordinary clinical observations, and by records of the ULF force BCG and the carotid pulse derivative.

The results were completely negative. Neither subjects nor observers could distinguish between the digitoxin and control periods. Statistical analysis disclosed no significant differences.

Surprised by the negative results, the authors asked the Food and Drug Administration to test the digitoxin used; it met all official chemical and biological requirements although it had failed to stimulate the frog heart in a type of test now discarded.

In the great majority of our subjects, their hearts, though not stimulated by digitalis, were markedly stimulated by mild exercise. This demonstrates clearly (1) that our failure to demonstrate digitoxin action in the majority cannot be attributed to incapacity of elderly hearts to respond to stimulation; (2) that the techniques used were fully capable of demonstrating cardiac stimulation when it occurred.

That digitalis glycosides benefit some types of diseased hearts more than others has long been known and all types were not represented in our study. Our negative results do not indicate that such drugs should never be tried in elderly persons in

normal rhythm our studies detected no harm from digitoxin administration Nevertheless, Mackenzie s skeptical view is strongly upheld by our negative results, and our findings contrast sharply with the therapeutic expectations of many doctors.

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The phonocardiographic assessment of myocardial function in the aged

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Whereas normal standards for cardiovascular performance are generally determined by the examination of young individuals, few hemodynamic data are available concerning myocardial contractility in the elderly. There is both clinical and pathologic evidence that myocardial changes occur with increasing age even in the absence of recognizable heart disease.[1-4] In fact, when heart failure does occur, a specific etiology is often not apparent,[1,5] and a presumptive diagnosis of arteriosclerotic heart disease is frequently made primarily because of the age of the patients.

Since there is generally no clinical indication for cardiac catheterization in this group and stress tests entail definite risks, indirect methods must be utilized to study cardiac function. The purpose of this study was to measure systolic time intervals as an indirect parameter of myocardial performance in the aged. Our results support the concept of an aging myocardium.

Methods

The subjects for this study were selected from the Chronic Disease Unit of the Coney Island Hospital, composed principally of elderly patients in need of nursing and custodial care. Two groups were studied, one with no clinical, electrocardiographic, or radiologic evidence of heart disease (group I) and the other with heart disease but no clinical evidence of congestive failure (group II). All patients chosen were in sinus rhythm and free of intraventricular conduction defects. For comparison, a third group composed of 18 younger healthy hospital employees was also evaluated (group III). All subjects received a complete physical examination and had a chest x-ray and electrocardiogram. None of the subjects studied was receiving digitalis. The sex distribution was similar in all 3 groups. Table I provides an analysis of the cardiac abnormalities in group II. None of these patients had hypertension (diastolic pressure above 90 mm. Hg) or evidence of congestive failure.

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Table I. Elderly subjects with heart disease

Finding	No. of patients
Congestive failure	0
Angina	1
ECG evidence of old infarction	3
S-T and T-wave abnormalities without Q waves	5
Isolated left axis deviation	4
Left ventricular hypertrophy	9
X-ray evidence of cardiac enlargement	16

The etiology of the heart disease was not always clear. Three patients had definite criteria for the diagnosis of coronary artery disease, while 5 others had S-T segment and T wave abnormalities consistent with myocardial ischemia and 4 had isolated left axis deviation beyond $-30°$. No specific etiology was apparent in the remaining 11 patients, all of whom had cardiac enlargement.

Heart sounds were recorded with a Sanborn No. 62 phonocardiogram at a paper speed of 75 mm. per second simultaneously with the electrocardiogram. A piezoelectric crystal microphone pick-up was used for the external monitoring of the carotid pulse. Tracings were taken at the point of maximal intensity of the first heart sound and the logarithmic technique was employed in order to record high frequency components of the first sound. All patients were studied at rest in the supine position and at the same time of the day.

From the tracings, the following intervals were measured (Fig. 1): (1) Q-S, the interval between the initial deflection of the QRS complex and the first major vibration of the first heart sound; ( ) S_1-CU, the interval between the first major vibration of the first sound and the onset of the carotid pulse upstroke; (3) Q-CU (pre-ejection period) Q-S + S_1-CU; (4) ejection period, the interval between the onset of the carotid upstroke and the incisura; (5) R-R interval and QRS duration. The Q-S, Q-CU, and S_1-CU intervals were read to the nearest 0.005 second, but

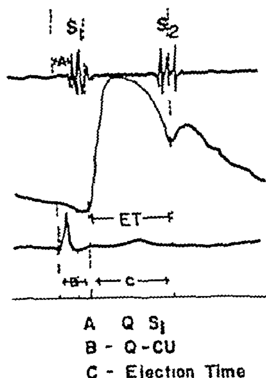


Fig. 1. The temporal relationships of the QRS complex, heart sounds and ejection period of the carotid pulse.

ejection time could be read accurately only to the nearest 0.01 second. The mean of 4 consecutive cardiac cycles was obtained for each parameter measured.

Results

As Table II shows, there was a mean difference in age of more than 40 years between our aged subjects and younger controls. It is interesting to note that the mean pre-ejection and ejection intervals were identical in groups I and II. On the other hand, the mean Q-S_1 interval and pre-ejection period were significantly longer ($p < 0.01$) in the elderly subjects than in the younger controls. Of the 40 elderly patients, 26 had Q-S_1 intervals and 29 had Q-CU intervals beyond 2 standard deviations from the mean values of the younger subjects. Since the mean R-R interval and QRS duration were very close in all 3 groups, the differences cannot be explained on the basis of cardiac rate or ventricular depolarization time. The S_1-CU interval was slightly longer and the ejection

Table II Systolic time intervals (seconds)

Group	Age	N of males	R-R	QRS	Q-S_1	S_1-CU	Q-CU	Ejection fraction
I (17 patients without heart disease)	78(67 to 88)	9	.74 ± .003 S.E.	.090	.075 ± .002 S.E.	.045 ± .003 S.E.	.120 ± .003 S.E.	[illegible] ± [illegible] S.E.
II (23 patients with heart disease)	77(67 to 96)	8	.78 ± .003 S.E.	.085	.075 ± .003 S.E.	.045 ± .003 S.E.	.120 ± .004 S.E.	.23 ± [illegible] S.E.
III (15 normal controls)	34(22 to 50)	6	.76 ± .003 S.E.	.080	.055 ± .003 S.E.	.035 ± .004 S.E.	.090 ± .006 S.E.	.30 ± [illegible] S.E.

was shorter in the elderly groups but these differences were not statistically significant.

Discussion

Cardiac findings in the aged have been the subject of several pathologic studies. Pomerance[5] in a review of a large consecutive series of aged hearts concluded that myocardial abnormalities were frequent even in the absence of prior cardiac signs or symptoms. Although ischemic heart disease was the most common finding, 10 per cent of the patients over the age of 80 had amyloid deposits in the myocardium.

There have been numerous reports of infiltration of brown pigmentation in aged hearts sometimes associated with atrophy. Strehler and associates[6] demonstrated that the accumulation of this lipofuchsin pigment within the myocardial fibers is progressive with advancing age. Although they found no correlation with prior cardiac disease or congestive failure, they thought it likely that this pigment interfered with myocardial efficiency because of the relatively large intracellular volume that it occupied.

There is clinical evidence to support the view that aging decreases the functional capacity of the myocardium. Dock[3] has pointed out that stresses such as hyperthyroidism, anemia, and hypertension commonly precipitate congestive heart failure in patients over 60 even in the absence of previous evidence of heart disease, but rarely in those under 25. He used the term "presbycardia" to describe this loss of functional reserve with aging. Andrus[1] found a fairly constant rise in the incidence of heart failure in hyperthyroidism with each succeeding decade.

The few hemodynamic studies have given disparate results. Resting stroke volume relative to oxygen consumption has been found to remain constant with aging in one study[7] and to decrease in another[8] and cardiac output during graded exercise has been variably reported as decreased[8] and increased.

One approach to the assessment of myocardial function is the measurement of the systolic time intervals. Weissler and co-workers recently demonstrated that there is a significant redistribution of the systolic time relationships in congestive heart failure. They found that the Q-S_1 and S_1-CU intervals were longer and the ejection period shorter in patients with congestive failure than in normal subjects with the same heart rate. This was true even for patients with clinically mild decompensation.

Recent studies[1,22] suggest that the timing and intensity of the first heart sound are related to the power and rapidity of ventricular contraction (first derivative of the pressure curve) as well as the diastolic tonus of the myocardium. Therefore, in the absence of intraventricular conduction delay and mitral stenosis (which impedes left ventricular filling)[8,11] a prolonged Q-S_1 interval reflects an impairment of myocardial contractility. Furthermore, this age-related decrease in contractility in our elderly subjects appears to be

the result of intrinsic deterioration of the cardiac muscle since it is not secondary to an increased left ventricular work load as is seen for example, in hypertension.[2]

The interval from the first heart sound to the onset of the carotid pulse (S-CU) depends on the rate of further development of myocardial tension until intraventricular pressure rises above aortic pressure and ejection occurs. It also includes the time required for transmission of the pulse to the carotid artery. Harrison and associates[6] reported a decrease in pulse transmission time and an increase in isovolumic relaxation time in elderly subjects and ascribed these changes to loss of elasticity of the aorta and left ventricle. The failure to find a significant prolongation of the S-CU interval in our subjects may be due to this decreased pulse transmission time, which could mask a delay in the development of myocardial tension. However, in contrast to Harrison and his associates, we found significant prolongation of the total pre-ejection period (Q-CU interval) in the aged.

Our results demonstrate an apparent age-related loss of myocardial reserve in the absence of obvious heart disease. This loss of contractility is consistent with the demonstration by Starr and Ogawa[17, 18] of a progressive decrease in the systolic (I J) wave of the ballistocardiogram and in the first derivative (rate of rise) of the brachial pulse, two other parameters of myocardial performance. Since the physical activity of our elderly subjects was somewhat limited in a chronic nursing unit, it is possible that some would have shown evidence of myocardial ischemia or decompensation under more stressful conditions.

Of additional interest is the fact that the presence of heart disease without congestive failure did not prolong the pre-ejection interval further in these elderly subjects. This implies that the chest x-ray and electrocardiogram are not sensitive indices of the functional capacity of the myocardium in the aged and that a generalized aging process occurs independently of obvious coronary disease or apparent cardiac enlargement.

It is clear that the influence of aging on the pre-ejection period must be considered when this measurement is used to distinguish between cardiac compensation and decompensation. Furthermore, we wonder whether the pre-ejection period may sometimes be prolonged in the presence of early myocardial disease at any age. It would be of interest to measure these intervals in young patients with primary myocardial and coronary heart disease and to determine whether they correlate with end-diastolic pressure measurement and the results of exercise tests. Perhaps delay in the onset of the first heart sound ($Q\text{-}S_1$) and prolongation of the pre-ejection period can become useful clinical indicators of mild myocardial dysfunction before overt decompensation occurs.

Summary

Phonocardiography was used to measure the time intervals from electrical excitation to the onset of the first heart sound ($Q\text{-}S_1$) and to the beginning of the carotid upstroke (Q-CU) as well as left ventricular ejection time in elderly subjects with and without apparent heart disease. The mean Q-S and Q-CU intervals were identical in the two groups but were significantly longer than in a group of young normal subjects. The results support the views that myocardial contractility decreases with age and that this aging process is independent of clinically recognizable heart disease.

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Cardiovascular complications in young patients taking psychotropic drugs

A preliminary report

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In recent years, reports have appeared in the medical literature regarding electrocardiographic changes produced by the administration of psychotropic agents to man[1-6] and to experimental animals[4,7,8] and some authors have demonstrated the association of arrhythmia and sudden death with long term phenothiazine therapy.[1] Electrocardiographic abnormalities have been reported with almost all the phenothiazine derivatives and also with the closely related compounds, imipramine and amitriptyline.[12] Ventricular arrhythmia and death caused by acute poisoning with thioridazine[13] and imipramine[14] have recently been reported. These few reports published in journals not regularly read by the internist or cardiologist have failed to alert these physicians to the cardiac complications which may ensue during long term administration of these drugs. In fact, one of the most comprehensive reports on the pharmacology and toxicology of the tranquilizers[15] gives scant mention to the cardiovascular complications and a recent article dealing with the toxic reactions described only the effects on the liver, eye, neurological system, etc., without mentioning cardiac or electrocardiographic effects. Yet in data obtained from a review of sudden death in 54 patients taking phenothiazines,[17] two thirds were under the age of 44, suggesting that drug-induced arrhythmias rather than arteriosclerotic coronary artery disease were responsible. This report emphasizes the point that death in patients taking phenothiazines occurs mostly in young people (Table I).

It is the purpose of this paper to describe young patients in whom cardiovascular or electrocardiographic abnormalities were encountered during prolonged treatment with phenothiazines or related compounds. Partial or complete correction of the abnormalities was accomplished in some patients by stopping the drug. Selective coronary angiography in one patient and myocardial biopsy in another revealed interesting information not heretofore reported.

Case reports

Case 1. J. W. L., a 23-year-old schizophrenic, was admitted in November, 1966, for depression, irritability, nervousness, and talk of suicide. From 1964 to

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*Table I. Sudden unexpected or unexplained death in 54 patients taking phenothiazines**

Age group	N	Per cent
15–24	3	5 6
25–34	16	29 6
35–44	16	29 5
45–54	13	24 6
55–64	3	5 6
65+	3	5 6
Total	54	100 0

Sex distribution: males, 40 (69 per cent); females, 18 (31 per cent). Mean age

*Compiled from data collected by J. E. Leestma, and K. L. Koenig. Arch. Gen. Psychiat. 18:137, 1968.

1965 he had bee taking 100 mg. of thioridazine daily nd 400 t 2 000 mg. of chlorpromazine daily for 6 months prior to admission. There was no family history of diabetes, hypertension, or heart disease. The physical examination was not remarkable. While in the hospital he was treated with phenothiazines and amitriptyline. An electrocardiogram (ECG) taken 10 days after admission was considered normal. T weeks later he noted palpitation while t h ng telev sion and then later that night awoke th sharp substernal chest pain lasting several hours. The ECG now revealed evidence of acut nferior wall nfarction (Fig. 1). The diagnosi wa supported by rise creatine phosphokinase (CPK) t 560 and serum glutamic oxalacetic transaminase (SGOT) to 78 nits, both enzymes subsequently f lling to normal alues. Because of his uncooperativ ttitude, treatment was less than ideal and he was discharged 2 months later till taking 200 mg. of chlorpromazine daily. Eighteen months later he was admitted t another hospital with a diagnosis of recurrent myocardial nfarction. In the interim he had been taking a variety of phenothiazine medications of unknow dosage. On transfer t this hospital 4 days later blood pressure was 90/66, the pulse 110, and temperature 101°F. Laboratory data again supported the diagnosis of acute infarction, the SGOT rising t 99 and CPK t 1,040 units before return ng t normal. The ECG (Fig. 2) howed loss of the R wav in Lead I and V_1, nd clockwise otation in the precordial leads when compared to the ECG taken in January 1967.

Case 2. L. B. M. 36-year-old asymptomatic Caucasian male, as admitted for evaluation of tachycardia nd left bundle branch block that appeared on the ECG. Between 1956 and 1962 he was treated with mephobarbital, diphenylhydantoin, and imipramine for nxiet and depression. In 1962 the chest x-ray was normal. From August, 1962, to December 1967 thioridazine, 100 mg. twice a day and imipramine 25 mg. t ice daily ere administered. On physical exam nation blood pressure was 120/90 nd pulse 130. A diastolic gallop was heard along the left sternal border. Laboratory tests revealed the following: CPK and SGOT enzymes were normal; cholesterol was 313 mg. per cent, triglyceride 200 mg. per cent, phospholipids 181 mg. per cent, and total lipids 635 mg. per cent. While in the hospital, psychotropic medication was discontinued and 2 weeks later the left bundle branch block and gallop rhythm disappeared. The serum cholesterol fell to 160 mg. per cent. Because of persistently abnormal ECG (T waves inverted in V_3, V_4, and V_5), selective coronary arteriography was performed which showed both coronary arteries and their major branches to be normal and widely patent. He was challenged again with thioridazine and imipramine separately (Fig. 3), each drug being given for one week with no change in ECG or clinical state. However intermittent left bundle block reappeared 6 months later hile he was taking both drugs.

Case 3. L. R. DeL., a 32-year-old Caucasian paranoid schizophrenic, was treated with fluphenazine since 1960. In 1965 he had normal ECG. From 1965 to 1967 he was given imipramine, chlorpromazine, and fluphenazine. In December 1966, he complained of chest pains od anxiety for which he was admitted on J n. 5 1967. His ECG showed pattern of old inferior wall myocardial infarction. Five days later he again developed chest pain. A rapid decrease in the level of serum cholesterol from 300 to 180 mg. per cent, and disappearance of his precordial pain coincided with discontinuation of the phenothiazines and im pramine but the ECG remained unchanged.

Case 4. W. J. S. 30-year-old nursing assistant, had marital trouble nd depression in 1965. He at self-treated with desipramine 25 mg. and nortriptyline, 25 mg. 3 times day. Physical examination then was unremarkable. In December 1965, he was found to have an enlarged heart on ray and on J n. 17 1966 he was admitted with trial fl tter and entricular rate of 150 per minute. He was electrically cardioverted to sinus rhythm, but flutter recurred while on amitriptyline, despite digoxin and qui idine. Since January 1967 he has been maintained on am triptyline, chlordiazepoxide, and thioridazine, nd his ECG shows frequent trial ectopic beats.

Case 5. F. M. O'B. a 41-year-old Caucasian man, was admitted because of pilonidal cyst. He had history of migraine for years and angina for 4 months. The ECG showed evidence of old anterior myocardial infarction. Chlorpromazine produced (1) elevation of CPK and SGOT enzymes and (2) evidence of new inferior all myocardial infarction after he was challenged with the drug (Fig. 4).

Case 6. J. R. L., a 29-year-old Caucasian male chronic schizophrenic, was hospitalized many times for psychiatric reasons since 1958. For 5 years he had been taking imipramine 50 mg. 4 times day and thioridazine trifluoperazine, 10 mg. twice a day and thioridazine 200 mg. 4 times day. I the year prior to admission he gained 60 pounds and in March, 1967 he developed progressive dyspnea on exertion, orthopnea, nd paroxysmal nocturnal dyspnea. The past history was negativ. he had no previous history of heart disease and he and his family denied that he drank to excess. Review of 5 years of hospital record failed to reveal ny mention of alcoholism.

On physical examination blood pressure as 100/78 nd pulse 100 beats per minute and regular. There was no neck ein distention but bilateral

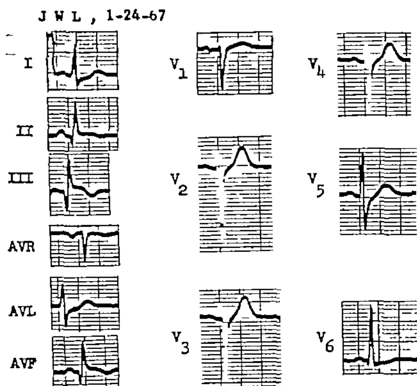


Fig. 1. Case 1. ECG showing evidence of acute inferior wall infarction.

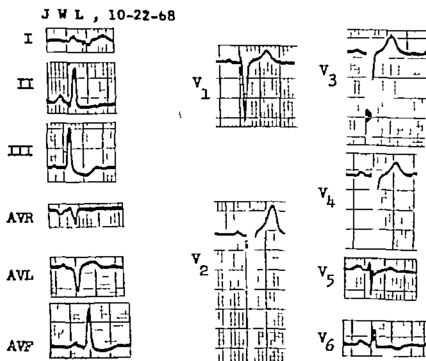


Fig. 2. Case 1. ECG 18 months later now shows loss of the R wa in Leads I and VL and clockwise rotation in the precordial leads.

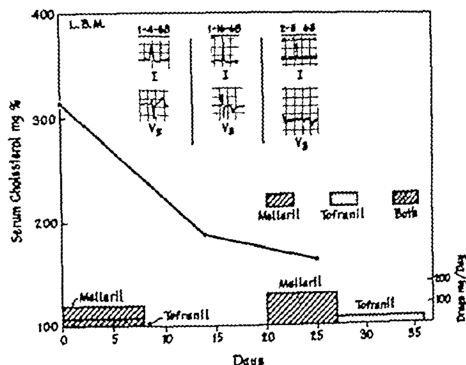


Fig. 3. Case 2. Mild hypercholesterolemia and left bundle branch block which disappeared when the drugs were discontinued but replaced by abnormal T waves suggesting ischemia. The block did not reappear when drugs were restarted separately but reappeared 6 months later while taking both drugs together. Note the coincidental decrease in serum cholesterol when drugs were stopped.

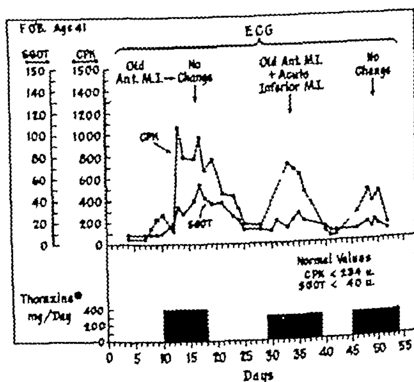


Fig. 4. Case 5. Striking rise in SGOT and CPK enzymes on three separate trials of chlorpromazine administration. Each rise is less prominent than the one before. Electrocardiographic evidence of acute inferior myocardial infarction appeared during the second trial.

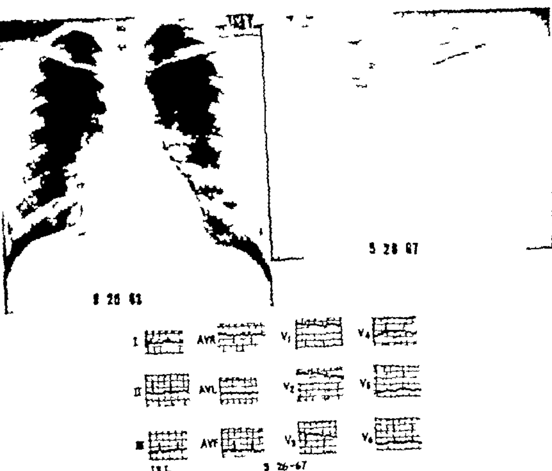


Fig. 5 Case 6. The chest x-ray in 1967 shows marked changes from the normal chest x-ray in 1963. There is cardiomegaly, pleural, and possible pericardial effusion and pulmonary congestion. The ECG of the same date shows sinus tachycardia and diffuse nonspecific T changes.

basilar râles were heard. On auscultation of the heart a ventricular gallop was heard but there were no murmurs. The abdomen was obese but no organs were palpable and there was no ascites. The lower extremities showed mild pitting edema. Chest x-ray showed cardiomegaly, pulmonary congestion, and pleural and probably pericardial effusion (Fig. 5). His ECG showed sinus tachycardia at a rate of 120 per minute and nonspecific T changes.

Laboratory data. Hemoglobin was 12.7 Gm., temporarily increased to 18.5 Gm. after profuse diuresis, but then promptly fell to 13 Gm. Other blood data included blood urea nitrogen (BUN), 22 mg. per cent; 2 hour post cibum sugar, 167 mg. per cent; cholesterol, 244 mg. per cent; bromsulphalein, 19 per cent retention in 45 minutes; alkaline phosphatase, 18.2 units; serum proteins, 8.7 Gm. per cent; serum electrolytes were normal. His vital capacity was 3.8 L. and 2.5 L. were expired in one second. Arterial gases showed pH, 7.40; pCO_2, 30 mm. Hg; and bicarbonate 18 mEq. per liter.

Hospital course. The phenothiazines were discontinued. The patient was placed on bed rest, a salt-restricted diet, and digitalis. He lost 34 pounds

Table II. Heart catheterization. Case 6. June 6, 1967

Parameters	*Rest*	*Exercise*
Cardiac output (L./min.)	5.7	6.4
Oxygen saturation (%)	96	97
Dye appearance time (sec.)	8.7	
Pressures (mm. Hg)		
Pulmonary capillary wedge	10	16
Pulmonary artery	34/16	43/19
Pulmonary artery (mean)	21	29
Right ventricle	30/6	
Right atrium	5	
Brachial artery	113/71	
Brachial artery (mean)	83	
Brachial artery dp/dt	875	
Pulmonary vascular resistance, dynes/sec./cm.[-5]	154	
Heart rate	103	118



Fig. 6. Case 6. Myofibers mainly seen in cross section, are spaced widely apart and contracted. The area on the right contains dark-staining lipochrome pigment (*LP*) amidst a cluster of closely packed mitochondria. Considering age of patient, the amount of this pigment appeared increased. Sarcoplasmic reticulum (*SR*) is generally dilated. Glycogen is abundant. (Magnification—2,808 X 4.)

in 7 days. Heart catheterization performed on June 6, 1967 after cardiac compensation was achieved, revealed the data shown in Table II. These findings may be interpreted as showing left heart failure on moderate exercise the edge pressure rising from 10 to 16 mm. Hg. Myocardial biopsy using a 1.2 mm. Mergh m needle was done without complication after completion of the catheterization procedure. The tissue prepared as previously described and examined RCA EMU-3G model electron microscope. Electron microscopic findings (Figs. 6 through 8) demonstrated separation of contracted myofibers by clusters of mitochondria, some of which appeared enlarged and bizarre in shape. Sarcoplasmic reticulum was dilated. Fat was present but not in excess. Glycogen granules were abundant and in one area (Fig. 8), they were enclosed in an irregularly shaped, double-membrane sac. Considering the age of the patient, degenerat pigment was present in excess e mou ts.

He was readmitted 15 months later after taking chlorpromazine continuously for 12 months, with recurrence of congestive failure gallop rhythm, and cardiomegaly. He improved with treatment but less dramatically than before and he was discharged.

Case 7. D. A. R. 22 year-old disturbed veteran, developed a marked flattening of T waves I the ECG taken 15 months after he began taking phenothiazines in variable quantities (Fig. 9). Auscultation revealed an intermittent gallop rhythm on mild exercise and chest roentgenogram demonstrated borderline cardiomegaly.

Pharmacology

The phenothiazine derivatives have a three-ringed structure in which 2 benzene rings are linked by sulfur and nitrogen. Compounds differ by having different side chains attached to positions 2 and 10 (Fig. 10). However all have similar pharmacologic actions and therapeutic applications. The most common effect of the phenothiazines is hypotension but the mechanism of the hypotensive action is poorly understood. Decrease in peripheral vascular resistance due to medullary vasomotor mechanism [1] and adrenolytic activity because of adrenergic blockade have been proposed as mechanisms of action.[9,18] In studies in dogs, fluphenazine and trifluoperazine in

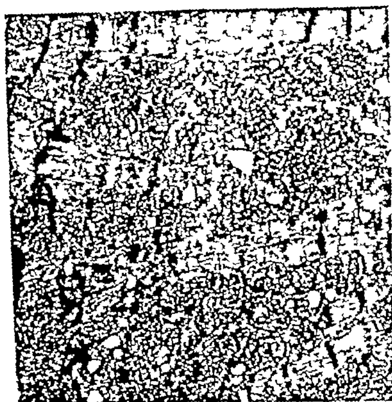


Fig. 7. Case 6. Except for widely spaced myofibers suggesting loss of contractile elements this area appears reasonably normal. (Magnification 4,260 × 4.)

doses of 1 mg. per kilogram were found to decrease systolic, diastolic, and mean arterial pressure with minimal elevation of the heart rate.[21] Also in dogs chlorpromazine in doses of 2 and 5 mg. has been found to produce initial hypotension followed by return to mean arterial levels and during the next 60 minutes, a secondary decline in blood pressure to hypotensive levels, mediated through its effect on the central nervous system.[22] Similar results were obtained with trifluoperazine in 251 schizophrenic men although the effect was mild when compared with the marked hypotensive effect produced by acetophenazine and imipramine.[23]

The phenothiazines are believed to compete with catecholamines for a binding site in the cell membrane causing a profound reduction in the tissue levels of exogenously administered H norepinephrine[24,25] by preventing its uptake and not by stimulating its release.[26] In fact, it has been found that this inhibition of tissue binding of norepinephrine by chlorpromazine produces unusually high blood plasma and urine levels of endogenous norepinephrine on occasions to values exceeding 7 μg per liter, a level only encountered in patients with pheochromocytomas undergoing hypertensive crisis.[27] These values were found curiously in exercising patients who had a fall in mean arterial blood pressure, a pronounced decrease in peripheral vascular resistance, and an abnormal increase in heart rate. Pretreatment with these drugs will block the adrenergic effect of epinephrine and the ordinary weak, vasodilating action of epinephrine becomes enhanced and paradoxically administration of this agent results in hypotension.[25]

The dibenzazepine compounds (imipramine and amitriptyline) have also a three ringed structure but lack the sulfur atom and the substitution of the side chain occurs only in position 10. These compounds have also been demonstrated to have sympatholytic activity producing a certain degr

Table III. Pharmacologic and ECG effects of phenothiazine and dibenzazepine compounds

Phenothiazines	*Imipramine-amitriptyline*
Pharmacologic effects	
Adrenolytic activity[illegible]	Adrenolytic activity and anticholinergic activity[illegible]
Reverses pressor response to epinephrine and prolongs pressor response to norepinephrine[illegible]	Amitriptyline reverses pressor response to epinephrine, imipramine potentiates pressor response to epinephrine[illegible]
Inhibits tissue binding of noradrenaline elevating the plasma levels of this catecholamine[illegible]	Inhibits tissue binding of H-norepinephrine, elevating plasma levels of this catecholamine[illegible]
Inhibits catecholamine depletion induced by metaraminol, guanethidine, and 6-hydroxydopamine[illegible]	Inhibits catecholamine depletion induced by metaraminol, guanethidine, and 6-hydroxydopamine[illegible]
Electrocardiographic findings	
Q-T, ST-T changes	Tachycardia
Blunt and notched T waves	A-V block, bundle branch block
↑ amplitude of U waves[1]	Shifting ventricular pacemaker[illegible]

S-T depression are quite characteristic.[illegible]

The literature has referred to cardiac arrhythmias and autonomic nervous system alterations induced by these drugs, but except for one report,[illegible] no mention of myocardial damage as manifested by cardiac enlargement or congestive heart failure has been noted. Nevertheless, in a recent study of patients taking 2 Gm. of chlorpromazine per day the cardiovascular complications were serious enough to require either reduction in dosage or elimination of the drug entirely in one third of the patients.[illegible] Although the evidence is only circumstantial, we suspect that these drugs in commonly used psychotherapeutic doses for prolonged periods are capable of producing a toxic cardiomyopathy which may or may not be reversible. In one patient, Case 6, the cardiomyopathy was severe enough to produce cardiomegaly, gallop rhythm, biventricular failure, and abnormal electrocardiographic changes. In Case 2, left bundle branch block disappeared soon after the drug was stopped. Case 5 developed evidence of acute myocardial infarction when he was challenged with chlorpromazine and myocardial infarction occurred in Case 1 while on large doses of chlorpromazine. Acute myocardial infarction occurring in a patient taking imipramine has been reported by Sloman[illegible] who also cited three additional cases. The evidence at hand is insufficient to determine whether or not these drugs predispose to early coronary artery disease in susceptible individuals. The young age of the patients involved and the severe coronary atherosclerosis found at autopsy[illegible] certainly raise questions in this regard. Moreover, the hypotensive action of the drugs may precipitate coronary insufficiency, myocardial infarction, or focal necrosis* in patients already suffering from coronary artery disease.

The demonstration of CPK and SGOT elevations on each of three challenges with chlorpromazine, to our knowledge, has never been reported.[illegible] Laboratory error and artifact were ruled out, the latter by the addition of the drug to the patient's plasma in vitro before enzyme determination. In view of this information, the appearance of acute infarct changes following the second drug challenge strongly suggests that the rise in enzymes indeed reflected damaged or necrotic myocardium.

In Case 6, the ultramicroscopic findings suggestive of muscle fiber destruction, increased glycogen deposition and clusters of mitochondria occupying space between fibers are similar to those found in alcoholic cardiomyopathy, where a metabolic alteration is believed to impair generation of energy for contraction. The negative inotropic action and decreased contractility

*Table I in reference 44 lists chlorpromazine as one of the drugs capable of elevating serum enzymes, but no evidence for this claim in the references cited by the authors could be found.

of heart papillary muscle exposed acutely to chlorpromazine also suggests an anti metabolic action.[47] The glycogen-filled sac seen in the biopsy is unique for to our knowledge, it has not been observed before in human myocardium. The amount of degenerative pigment present presumably lipochrome was greater than what was expected for the patient's age and may be the result of phenothiazine ingestion.[48] In view of the persistent cardiomegaly gallop rhythm, and recurrent heart failure over a two year period complete recovery in this patient seems doubtful.

In Cases 2 and 3 serum cholesterol decreased sharply following discontinuation of the psychotropic drugs from 313 to 160 mg per cent and from 300 to 180 mg per cent, respectively Whether serum cholesterol is reversibly increased by these drugs is not known and probably should be further investigated It is unlikely that changing to the hospital diet alone could lower cholesterol in such a sharp manner

There are conflicting reports regarding phenothiazines and arrhythmias. Experimentally thioridazine which has quinidine like activity can antagonize acetylcholine-induced atrial fibrillation and is capable of converting atrial flutter to sinus rhythm.[49] Epinephrine-induced arrhythmias can also be aborted with phenothiazines, and pretreatment with phenothiazine raises the dose of epinephrine required to produce the arrhythmia.[50] Arrhythmias developing in patients treated with large doses of thioridazine have been well documented [11] and the quinidine-like activity of the drug has been pointed out. Thus, thioridazine like quinidine, can produce certain electrocardiographic changes namely increased Q-T interval, bifid changes in T waves, and even ventricular tachycardia. Hypokalemia has been mentioned as a possible contributing factor although when studied serum potassium and other electrolytes were found to be normal [54] Calcium ion movements and myocardial contractility are inhibited by chlorpromazine in experimental preparations [51] thus raising the question of whether such an action might play a part in human disease.

The underlying biochemical basis for the toxicity is unknown Preliminary studies in humans suggest that the urinary excretion of magnesium is increased during oral administration of thioridazine suggesting possible alterations in the magnesium-dependent sodium potassium ATPase system Experiments using rat brain have demonstrated sodium potassium ATPase inhibition by substituted phenothiazines.[52] Negative inotropic action has been demonstrated on cat papillary heart muscle exposed to chlorpromazine.[47] A mucopolysaccharide material has been shown to be deposited in the small arterioles of the subendocardial region of the heart in patients dying suddenly after many years of phenothiazine therapy [53] If small vessel disease is confirmed while demonstrating absence of occlusive disease in major coronary artery branches, focal ischemia or necrosis may well explain the arrhythmias, sudden death and diffuse cardiomegaly that may occur with the long term use of these drugs.

In conclusion phenothiazines and related drugs can produce alterations in the electrocardiogram in 50 to 70 per cent of subjects taking large doses for prolonged periods in certain cases, and can cause toxic cardiomyopathy manifested by cardiomegaly biventricular failure and arrhythmias. The mechanisms responsible for these abnormalities are unknown Three likely possibilities are (1) disturbance in energy production by affected mitochondria as judged by their ultramicroscopic appearance (2) focal ischemia and necrosis resulting from deposition of mucopolysaccharide material in small arteries and arterioles[53] and (3) disturbance in myocardial or plasma catecholamine concentration The reversibility of these lesions after discontinuation of the drug is questioned One patient continues to have recurrent bouts of congestive heart failure Quite frustrating has been the fact that in the majority of patients these drugs must be continued because of severe psychiatric disturbance making impossible a more complete evaluation of the cause-effect relationship between these compounds and the cardiac syndrome produced. Some psychiatrists have found haloperidol (Haldol) and its fluoride analogue trifluperidol a nonphenothiazine drug without known cardiac toxicity satisfactory substitutes for the pheno-

thiazines in chronic schizophrenic individuals.[14]

Summary

Seven cases are presented in whom cardiac arrhythmias, myocardial failure, or conduction disturbances or significant electrocardiographic changes occurred during prolonged administration of phenothiazines and related compounds, imipramine and amitriptyline. A 29-year-old man developed recurrent biventricular congestive heart failure after prolonged phenothiazine and imipramine administration. Myocardial biopsy material examined in the electron microscope revealed structural abnormalities of mitochondria suggesting a metabolic basis for the cardiomyopathy.

I am grateful to Mrs. Candad Go for technical assistance in preparation of material for electron microscopic examination.

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Experimental and laboratory reports

Effect of ethanol on metabolism and function of perfused rat heart

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The possibility of an association between chronic and excessive consumption of ethanol and myocardiopathy has been the subject of several recent studies.[1-4] Although the evidence suggests that chronic alcoholism might result in significant changes in myocardial metabolism structure and mechanical activity it remains to be elucidated whether these effects are directly caused by ethanol or whether they are the indirect result of associated nutritional and metabolic disorders accompanying chronic alcoholism

In an attempt to evaluate the effect of ethanol on myocardial metabolism and function the following experiments were performed on the isolated perfused rat heart (1) Ethanol was added to the perfusate of hearts from normal rats (acute experiments) (2) Rats were given ethanol for 18 months (ethanol treated) and the subsequent metabolism and function of the isolated hearts were studied both in the presence and absence of ethanol in the perfusate (chronic experiments)

The results obtained indicate that high concentrations of ethanol are capable of affecting myocardial mechanical activity in both acute and chronic experiments. Furthermore ethanol produced significant changes in the palmitate metabolism of normal and ethanol treated rat hearts by stimulating palmitate incorporation into tissue lipids.

Methods

Female albino rats (200 to 250 grams) of the Wistar strain were used in the acute experiments in which the effect of ethanol on myocardial metabolism and function was determined. The chronic experiments were performed on similar rats which received 15 per cent ethanol as the only source of drinking water for 18 months. The growth rate of these rats was similar to that of a series of control rats receiving water and kept under identical circumstances. This was shown by a similar increase in body weight during the course of the experiment and similar body and heart weights when sacrificed. All animals were fed *ad libitum* until decapitation

After decapitation the hearts were re-

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moved and arrested in ice-cold saline mounted onto a cannula and perfused for 30 minutes in a closed recirculating system.[14] A modified Krebs-Henseleit buffer[17] was used as perfusion fluid. Substrates added to the bicarbonate buffer were chromatographically pure glucose U-C^{14} 10 mm, sodium pyruvate 1-C^{14} and 3-C 6 mm, palmitic acid 1-C^{14} 0.7 mm, sodium acetate 2-C^{14} 5 mm, and ethanol 2-C^{14} 25 mm (obtained from Radiochemical Centre, Amersham, England). Albumin-bound palmitate was prepared as described before.[14] Absolute ethanol (BDH Analar grade) was added directly to the perfusion fluid.

Measurement and calculations for glucose uptake, pyruvate uptake and production, lactate production, titratable and C^{14} fatty acid uptake, incorporation of palmitate C^{14} into tissue lipid, residual cardiac glycogen, $C^{14}O$ collection from gas and liquid phases, $C^{14}O$ production, uptake of radioactivity from acetate 2-C, radioactivity assay, and myocardial ATP, ADP, inorganic phosphate (Pi), and creatine phosphate (CrP) were as described before.[14] The ethanol concentration of the perfusate was determined both chemically by a microdiffusion method and enzymatically using Boehringer test kits (Boehringer C. F. & Soehne GmbH, Mannheim) for alcohol determination (UV test with ADH and NAD).

Myocardial oxygen uptake was determined by analysis of the perfusate entering and leaving the heart for oxygen content and simultaneous measurement of coronary flow rate.[36] Measurements were made every 10 minutes over a 30 minute period and the mean oxygen uptake calculated for each heart. Perfusate oxygen content was determined by the Eschweiler Combi Analysator for gases (Model CA/3).

The mechanical activity of the isolated hearts was determined using a modified Langendorff perfusion assembly and myographic differential force transducer as described before.[21] This preparation was capable of performing both isotonic and isometric contractions.[22] All measurements were done with a constant preload produced by a 10 Gm. weight. Measurements of work performance included the determination of peak height of developed tension (PH) in millimeters, the tension time index (TTI) in milligram-seconds obtained by planimetric integration of the area under the systolic curve, and also tension time per minute (TTM).[23] Contractility indices were obtained by the measurement of the maximum rate of rise of developed tension (dp/dt_{max}) in milligram-seconds and the time to peak height of developed tension (t PH) in microseconds. The degree of stress relaxation (SR) as measured by the increase of resting length[21] was recorded. Measurement of work performance and contractility were done as before at each 5 minute interval over a 30 minute perfusion period.

In order to determine the correct reference material for the chronic experiments the total nitrogen, noncollagen nitrogen, nonprotein nitrogen, and noncollagen protein nitrogen contents of both control and ethanol treated hearts were determined as described in a previous report.[14] No significant difference was found in the noncollagen protein nitrogen content (control hearts 18.70 ± 0.41 mg. per gram of wet weight (17), ethanol treated hearts 17.95 ± 0.27 mg. per gram of wet weight (23) and wet weight was used as a reference base).

Results are expressed as mean ± SEM (number of observations). P values are derived from the Student t test.[25]

Results

Metabolism of ethanol 2-C^{14} by the perfused rat heart. Preliminary experiments were performed to determine whether ethanol was metabolized by the perfused rat heart. Using ethanol 2-C^{14} (25 mm.) as substrate no detectable amount of ethanol disappeared from the perfusate and no $C^{14}O$ was produced.

Acute experiments. Effect of ethanol on metabolic patterns. Palmitate 1-C metabolism by the perfused rat heart was unchanged in the presence of 100 mm of ethanol (Table I). Although 20.0 mm of ethanol had no effect on palmitate-C uptake, the percentage of palmitate uptake incorporated into tissue lipids was significantly increased ($p < 0.001$) while the percentage of incorporation into $C^{14}O_2$ was decreased ($p < 0.01$). Oxygen uptake

*No. in parentheses indicates no. of animals.

Table I The effect of ethanol on the metabolism of palmitate 1 C^{14} (0.7 mm) by the perfused rat heart

Ethanol concentration (mm)	Palmitate-C^{14} uptake*	$C^{14}O_2$ formation	Recovery of palmitate-C^{14} as tissue lipids*	% of palmitate uptake found in tissue lipids	% of palmitate uptake converted to $C^{14}O_2$	Oxygen uptake†
0	4 15 ± 0 33 (15)	2 03 ± 0 17 (15)	0 96 ± 0 05 (15)	20 ± 2	53 ± 4	47 77 ± 2.06 [illegible]
100	4 20 ± 0 36 (9)	2 29 ± 0 26 (9)	0 88 ± 0 08 (9)	22 ± 4	55 ± 6	43 73 ± 3 13 [illegible]
200	3 68 ± 0 18 (15)	1 28 ± 0 19 (15)	1 64 ± 0 09 (16)	43 ± 4	35 ± 4	50 44 ± 3 05 [illegible]
	$p < 0.3$	$p < 0.01$	$p < 0.001$	$p < 0.001$	$p < 0.01$	

Nos. in parentheses indicate no. of animals studied
P values indicate significance of difference from control.
*Expressed as μmoles palmitate equivalent per gram of wet weight per 30 minutes.
†Expressed as μl per gram of wet weight per minute.

with palmitate as substrate was not affected by ethanol.

Both 100 and 200 mm ethanol had no effect on pyruvate uptake and $C^{14}O_2$ formation with pyruvate-3-C^{14} (6 mm) as substrate. (Pyruvate uptake control 48 34 ± 2 17 100 mm 51 29 ± 2 10 200 mm 45 59 ± 3 0 $C^{14}O$ production control 10.83 ± 1 34 100 mm. 13.59 ± 1 51 200 mm 10 42 ± 1 42) Lactate production however was depressed by 200 mm of ethanol (Control 23 98 ± 1 07 100 mm. 22 07 ± 0 73 200 mm 18 06 ± 1 08 $p < 0.005$) Oxygen uptake with pyruvate as substrate was unaffected by 200 mm ethanol

Myocardial metabolism of glucose U-C^{14} (10 mm.) was unchanged in the presence of 100 and 200 mm ethanol.† Glucose uptake production of $C^{14}O_2$ lactate and pyruvate incorporation of glucose U-C^{14} into glycogen as well as residual glycogen contents were similar to control values. Furthermore, ethanol (100 and 200 mm) had no effect on the metabolism of acetate 2-C^{14} (5 mm) by the perfused rat heart, the uptake of acetate 2-C^{14} and $C^{14}O$ production being unchanged by ethanol.‡

The ATP ADP CrP and Pi contents of the hearts were unchanged after perfusion with 100 mm of ethanol (Table II) Perfusion with 200 mm of ethanol resulted in a significant depression in ATP and Pi contents.

Chronic experiments Metabolism of hearts from ethanol-treated rats and the additional effect of ethanol in the perfusate. In this section the results of two series of experiments are combined. First, the effects of long-term administration of ethanol on the substrate metabolism of rat hearts were compared with those of control hearts. In these experiments, the hearts of rats of the same age and weight as the ethanol treated group were studied as controls. The metabolism of these control hearts did not differ significantly from that of the younger control group in the acute experiments. Therefore the metabolism of the ethanol-treated hearts were compared with the control hearts in the acute experiments. Second the effects of 100 and 200 mm. of ethanol in the perfusate were determined on the metabolic patterns of these ethanol-treated hearts.

The pattern of palmitate metabolism in the hearts of rats that had been on an ethanol diet for 18 months (Table III) showed significant differences when compared to the control hearts of the acute experiment (Table I) Palmitate-C^{14} uptake of ethanol treated rat hearts, with no ethanol added to perfusate did not differ significantly from those of control rats. Recovery of palmitate-C^{14} as tissue lipids were significantly higher in the ethanol-treated hearts the decrease in $C^{14}O$

*Results expressed as μmoles of pyruvate equivalents per gram of wet weight per 30 minutes Eight hearts were studied in each series.
†Fourteen hearts were studied in each series.
‡Eight hearts were studied in each series.

Table II *The effect of ethanol on the ATP ADP CrP and* P_i *contents of the perfused rat heart (substrate, glucose 10 mm.)*

Ethanol concentration (mm.)	*ATP*	*ADP*	*CrP*	*P*
0	3 79 ± 0 30 (12)	1 04 ± 0 10 (12)	4 15 ± 0 27 (12)	6 65 ± 0 53 (12)
100	4 33 ± 0 41 (12)	1 08 ± 0 14 (12)	3 70 ± 0 26 (12)	6 73 ± 0 48 (12)
200	2 89 ± 0 10 (6)	0 83 ± 0 08 (6)	4 38 ± 0 27 (6)	4 77 ± 0 30 (6)
	p <0 02			p <0 01

Nos. in parentheses indicate no. of animals.
Values are expressed as µmoles per gram of wet weight.

Table III *The metabolism of palmitate-1-*C^{14} *(0.7 mm.) by ethanol-treated rat hearts and the effect of 100 and 200 mm. of ethanol*

Ethanol concentration in perfusate (mm.)	*Palmitate-*C^{14} *uptake*	$C^{14}O_2$ *formation*	*Recovery of palmitate-*C^{14} *as tissue lipids*	*% of palmitate uptake incorporated into tissue lipids*	*% of palmitate uptake converted to* $C^{14}O$
0	4 07 ± 0 54 (19)	1 64 ± 0 21 (19)	1 50 ± 0 13 (19)	34 ± 3	37 ± 5
100	3 50 ± 0 18 (4)	1 64 ± 0 68 (4)	1 59 ± 0 12 (4)	46 ± 5	46 ± 9
200	4 11 ± 0 06 (7)	0 73 ± 0 11 (7)	1 84 ± 0 12 (7)	45 ± 3	18 ± 3
		p < 0 001	0 1 > p > 0 05	p < 0 02	p < 0 005

Nos. in parentheses indicate no. of animals.
P values indicate significance of difference from control.
Results are expressed as µmoles of palmitate equivalent per gram of wet weight per 30 minutes.

production was not significant, but the S.E.M.'s were unusually large (palmitate-C^{14} uptake control 4.15 ± 0.33 ethanol treated 4.07 ± 0.54 $C^{14}O_2$ production control 2 03 ± 0 17 ethanol treated 1 64 ± 0.21 tissue lipids control 0 98 ± 0.05 ethanol-treated 1.50 ± 0 13 p < 0 001) The percentage of palmitate-1-C^{14} uptake incorporated into tissue lipids was significantly higher in the ethanol treated group (control 26 ± 2 per cent, ethanol treated 34 ± 3 per cent p < 0 05) The percentage of palmitate-1-C^{14} uptake incorporation into $C^{14}O$ was significantly lower in the ethanol-treated rats (control 52 ± 4 per cent, ethanol-treated 37 ± 5 per cent p < 0 05)

The results obtained by addition of 100 and 200 mm. ethanol to the perfusate of the ethanol-treated hearts (Table III) showed the same tendency as those achieved in acute experiments on untreated hearts. $C^{14}O$ formation was depressed, while the incorporation of palmitate-C^{14} into tissue lipids was increased by 200 mm. of ethanol. Recovery of palmitate label however was depressed with 200 mm ethanol.

Pyruvate uptake and lactate production by ethanol-treated rat hearts did not differ significantly from those of control rats. As in the acute experiments, ethanol had no effect on pyruvate uptake and $C^{14}O$ production of the ethanol treated hearts. In contrast to the acute experiments, 200 mm. of ethanol had no effect on lactate production in the ethanol-treated hearts.

Oxygen uptake by the ethanol treated rat heart was similar to those of control

Table IV The effect of ethanol on the mechanical performance of control rat hearts (substrate

Ethanol concentration (mm.)	*Coronary flow rate (ml./min.)*	*Heart rate/min*	*Stress relaxation (mm.)*
Time 0 to 15 minutes			
0 (8)	9 88 ± 0 47	198 ± 5	37 59 ± 6 11
100 (8)	10 65 ± 0 24	213 ± 6	30 18 ± 3 19
p		<0 05~0 1	
200 (8)	10 51 ± 0 52	240 ± 3	21 75 ± 2 95
p		<0 001	<0 05
Time 15 to 30 minutes			
0	7 01 ± 0 40	171 ± 4	34 09 ± 12 09
100	8 55 ± 0 44	192 ± 3	33 93 ± 5 43
p	<0 025	<0 001	
200	9 05 ± 0 64	216 ± 3	36 23 ± 8 55
p	<0 02	<0 001	

Nos. in parentheses indicate no. of animals.
"P" values indicate significance of difference from control.

Table V Mechanical performance of control and ethanol-treated rat hearts (substrate glu

Heart	*Coronary flow rate (ml./min.)*	*Heart rate/min*	*Stress relaxation (mm.)*
Time 0 to 15 minutes			
Control (8)	9 41 ± 0 52	240 ± 4	8 53 ± 1 70
Ethanol-treated (8)	10 29 ± 0 65	220 ± 7	6 15 ± 2 12
p_1		<0 05	
Ethanol-treated + 200 mm. ethanol (8)	9 30 ± 0 46	208 ± 11	9 30 ± 3 48
p†			
Time 15 to 30 minutes			
Control	6 97 ± 0 37	219 ± 5	9 47 ± 2 19
Ethanol-treated	7 78 ± 0 61	200 ± 8	10 52 ± 3 10
p_1			
Ethanol-treated + 200 mm. ethanol	6 40 ± 0 44	214 ± 3	13 93 ± 6 59
p†			

Nos. in parentheses indicate no. of animals.
*Significance of difference between control and ethanol-treated groups.
†Significance of difference between ethanol-treated group and ethanol-treated + 200 mm. of ethanol.

hearts with pyruvate as substrate. As in the acute experiments, addition of 200 mm of ethanol had no effect on the oxygen uptake of ethanol-treated hearts (unpublished observations). The high energy phosphate content of the ethanol treated rat hearts did not differ from that of control hearts (Table II) ATP 3.37 ± 0.29 (6) ADP 1 69 ± 0.86 (6) CrP 4.80 ± 0 50 (6) The inorganic phosphate content of the ethanol treated hearts was significantly lower than that of the control hearts (4 06 ± 0 39 and 6 65 ± 0 53 respectively p < 0 005)

Addition of 100 mm of ethanol to the perfusion fluid had no effect on the concentration of these compounds in ethanol-treated hearts.

Effect of breakdown products of ethanol on myocardial metabolism. Although ethanol was not metabolized by the heart, the increased concentration of its two break

cose 10 mm)

Peak height (mm.)	*TTI* (mg sec)	*TTM* (mg sec./min)	*dp/dt$_{max}$* (mg./sec)	*t-PH* (μsec.)
104 15 ± 6 02	2085 ± 124	406 054 ± 23 018	526 ± 35	109 ±
63 7 ± 5 4	1228 ± 100	256 890 ± 19 745	310 ± 35	106 ± 1
<0 001	<0 001	<0 001	<0 001	
38 52 ± 3 02	641 ± 82	152 099 ± 19 907	253 ± 42	95 ± 2
<0 001	<0 001	<0 001	<0 001	<0 001
118 72 ± 5 42	2236 ± 119	376 142 ± 17 509	660 ± 31	103 ± 1
107 8 ± 7 7	1929 ± 134	365 561 ± 22 793	602 ± 43	98 ± 1
				<0 005
59 36 ± 6 72	951 ± 107	204 985 ± 23 682	417 ± 52	90 ± 2
<0 001	<0 001	<0 001	<0 005	<0 001

m.)

Peak height (mm)	*TTI* (mg sec)	*TTM* (mg sec./min.)	*dp/dt$_{max}$* (mg /sec)	*t PH* (μsec)
50 36 ± 2 92	817 ± 64	189 949 ± 10 546	214 ± 10	92 ± 2
43 86 ± 2 88	743 ± 45	165 953 ± 12 205	183 ± 13	99 ± 2
				<0 05
32 84 ± 4 17	515 ± 66	111 624 ± 16 081	143 ± 19	96 ± 3
<0 05	<0 02	<0 02	<0 01	
46 08 ± 3 71	661 ± 56	140 515 ± 9 687	222 ± 15	83 ± 1
39 24 ± 3 57	627 ± 57	123 785 ± 11 199	178 ± 15	93 ± 2
			0 05>p<0 10	<0 001
31 87 ± 4 47	456 ± 70	94 633 ± 15 242	157 ± 21	83 ± 1
				<0 001

down products, acetaldehyde and acetate, in blood after alcohol ingestion might affect myocardial metabolism and function in vivo.[14,24,25] The effect of acetaldehyde was therefore studied on myocardial metabolism in the perfused rat heart. The effect of acetate on myocardial glucose[22,23] and palmitate[29] metabolism has already been studied.

Acetaldehyde (1 7 mm) had no significant effect on glucose or pyruvate metabolism by the perfused rat heart while palmitate-C[14] recovery as tissue lipids was unchanged.

Mechanical activity. The effect of ethanol (100 and 200 mm) was studied on the mechanical activity of two groups of hearts (1) control hearts (2) ethanol treated hearts. To determine whether long term administration of ethanol had an effect on the mechanical performance, the different parameters were compared with

a control group of the same age (the control hearts of group 1 being of a younger age group) The mechanical parameters of these two groups were measured every 5 minutes over a 30 minute perfusion period Mean values were calculated for each 15 minute period and summarized in Tables IV and V

The results obtained in the control experiments showed that age with associated change in heart size was an important factor in determining the mechanical activity of the perfused heart. Stress relaxation was greater and tension development and contractility were higher in the young animals (group 1)

GROUP 1 CONTROL HEARTS (TABLE IV) Ethanol (100 and 200 mm) had no effect on the coronary flow rate during the first 15 minutes of perfusion but increased it during the last 15 minutes while the heart rate was increased significantly throughout the perfusion period Perfusion with 200 mm of ethanol decreased stress relaxation significantly Both 100 and 200 mm of ethanol depressed work performance and contractility during the first 15 minutes of perfusion Peak height of developed tension (PH) tension time index (TTI) tension time per minute (TTM) as well as dp/dt_{max} were significantly lower when compared with the control group The mechanical performance of hearts with 100 and 200 mm of ethanol in the perfusate improved during the last 15 minutes of perfusion. However the depressant effect of 200 mm of ethanol on work performance and contractility remained significant.

GROUP 2 ETHANOL TREATED HEARTS (TABLE V) Comparison of the mechanical performance of control and ethanol treated hearts indicated that long term administration of ethanol had little effect on myocardial work performance and contractility in the rat Heart rate was significantly lower in the ethanol treated group during the first 15 minutes, but no change was observed during the remainder of the perfusion period PH TTI TTM and dp/dt_{max} were not different for ethanol treated hearts when compared with the control hearts. Suggestive evidence of an effect on myocardial contractility was forthcoming by the increase in t PH of the ethanol treated hearts

Addition of 200 mm of ethanol to the ethanol treated hearts resulted in a significant depression in PH TTI TTM and dp/dt_{max} during the first 15 minutes of perfusion. However no difference was observed during the last 15 minutes of perfusion. Time to peak height of developed tension was reduced a measurement which was probably affected by the reduction in PH

Discussion

The concentrations of ethanol used in this study (100 and 200 mm.) are high compared to those occurring in vivo in humans after ingestion of large amounts of ethanol However most of the studies on the effects of ethanol on myocardial function in experimental animals have been performed at ethanol concentrations ranging between 110 and 1,300 mg per cent.[5-8,21]

The results obtained indicate that although 200 mm of ethanol induces certain changes in the metabolism and function of isolated rat heart, it does not have a toxic effect.

Effect of ethanol on metabolic patterns. The results obtained indicate that ethanol (100 and 200 mm) had no effect on the metabolism of glucose-U-C^{14} acetate 2-C^{14} as well as the oxygen uptake of the perfused rat heart. Furthermore prolonged ethanol treatment had no deleterious effect on Krebs cycle oxidations in the rat heart, since no difference could be demonstrated between the oxygen uptake of normal and ethanol treated rat hearts. These results show that high concentrations of ethanol have no toxic effect on glycolytic as well as Krebs cycle enzyme systems in the rat heart. This is substantiated by the finding that higher concentrations of ethanol (300 and 600 mm) had no effect on the endogenous oxygen uptake of heart tissue slices (Lochner unpublished observations)

It has been postulated that ethanol might change membrane permeability thereby affecting intracellular metabolism[7] and studies on frog skeletal muscle showed that ethanol has a deleterious effect on membrane function.[22] However changes in membrane permeability if present in these hearts, did not affect uptake of the myocardial substrates studied

The finding that ethanol-administration

resulted in a significant depression of lactate production, while pyruvate uptake and $C^{14}O$ production remained unchanged, was unexpected and cannot be explained by the present studies. Further studies are necessary to elucidate this problem.

Ethanol (200 mm.) caused a significant change in the pattern of palmitate metabolism by the perfused normal as well as ethanol-treated rat heart, viz., an increased incorporation of palmitate-C^{14} into tissue lipids. Furthermore, the pattern of palmitate metabolism in the ethanol-treated heart (no ethanol in perfusate) was similar to that of a control heart with 200 mm. of ethanol and the possibility exists that long term administration of ethanol has the same effect in vivo as acute administration in vitro, resulting in a permanent change in palmitate metabolism. Since Krebs cycle activity is unaffected both in normal and ethanol treated hearts, the increase in palmitate incorporation into tissue lipids might be due to direct stimulation of palmitate esterification by ethanol. Since long-chain free fatty acid is a major fuel for the isolated heart, a decrease in its rate of oxidation indicates that some other endogenous substrate (e.g., triglyceride or glycogen) has become the major source of energy.

The acute and chronic effects of ethanol on myocardial free fatty acid metabolism show a similarity to those reported for liver. Ethanol decreases the rate of palmitate-C^{14} incorporation into $C^{14}O_2$ in vivo[illegible] and in vitro in liver slices[illegible] and stimulate incorporation into tissue lipids.[illegible] Livers of ethanol treated rats in comparison with control livers incorporate more free fatty acids into triglycerides.[illegible] The results obtained in this study indicate that a similar process might occur in the hearts of ethanol treated rats. It has also been shown that ethanol treatment results in a 00 per cent increase in the myocardial triglyceride content.[illegible] Furthermore, electron microscopic observations on hearts of patients with alcoholic myocardiopathy indicated numerous lipid droplets, consisting mostly of triglycerides.[illegible]

Since sarcosomal oxidative phosphorylation was unaffected by 200 mm. of ethanol (Lochner, unpublished observations), the reduction in ATP content of control hearts after addition of ethanol must be due to another mechanism. The finding of a reduced myocardial ATP content, while the phosphocreatine content remained normal, was surprising and might possibly be attributed to a block of transfer between ATP and phosphocreatine. It has also been shown that acute administration of ethanol to rats might result in reduction in hepatic ATP content.[illegible] The reduction in myocardial Pi content in the acute experiments as well as in the ethanol treated hearts might be due to release from the myocardium. Selective release of phosphate and potassium ions from the myocardium after ethanol has been reported in dog hearts.[8] Furthermore, the serum phosphorus of alcoholics has been found to be reduced.[44]

Since a large number of the metabolic effects of ethanol are mediated through the significant increase in $NADH_2/NAD$ ratio during ethanol metabolism,[*] it was necessary to determine whether rat heart tissue could metabolize ethanol. Although the ability of a large number of tissues to metabolize ethanol has been investigated thoroughly,[46,47] little is known about the ability of heart tissue. Alcohol dehydrogenase has been claimed to be present in the coronary sinus blood of chronic alcoholics and in the myocardium of rats not treated with ethanol. However, other investigators failed to demonstrate ADH activity in the rat myocardium.[illegible] The results obtained in this study indicate that ethanol-2-C^{14} was not metabolized to any measurable extent by both the perfused rat heart and tissue slices (Lochner, unpublished observations). The biochemical effects of ethanol, therefore, appear to be due to a direct effect and not to the consequence of a change in $NADH_2/NAD$ ratio or the accumulation of breakdown products such as acetaldehyde and acetate.

The metabolic changes produced by ethanol on the isolated perfused rat heart do not agree with those reported in in vivo experiments on humans and dogs. It has been suggested that there might be an impairment of the citric acid cycle in chronic alcoholism.[illegible] However, oxygen

*NAD and $NADH_2$, oxidized and reduced forms of nicotinamide-adenine dinucleotide.

uptake of the ethanol treated hearts was normal indicating a normal oxidative capacity. Myocardial extraction[4,8,34] of free fatty acids are significantly decreased by ethanol while plasma triglycerides become the predominant myocardial substrate. Unal, Webb and Cook[34] reported progressive metabolic acidosis suggesting that ethanol may interfere with aerobic metabolism. Apart from the effect of ethanol on heart lipoprotein lipase[35] and on cell permeability to exogenous triglyceride it appears as if most of the in vivo effects of ethanol on myocardial metabolism might be the consequence of the various extracardiac metabolic effects of ethanol.

Effect of ethanol on mechanical performance. The results obtained indicate that ethanol directly exerts a negative inotropic effect on the control rat heart (Table IV). No significant difference, however, was observed in the work performance of the isolated hearts after prolonged ethanol administration when compared with control hearts (Table V). The finding of an increased time to peak height is suggestive evidence of an impairment in contractility. Addition of ethanol to these ethanol treated hearts resulted in a marked diminution of all parameters of tension development as well as dp/dt$_{m}$ during the first 15 minutes. No significant change, however, was observed during the remainder of the perfusion period.

According to these results it would appear that long term ethanol administration not only has no definite effect on myocardial mechanical performance, but a certain degree of alcohol adaption has occurred. First, ethanol does not affect the mechanical activity of the ethanol treated hearts to the same extent as the control hearts. Second, 200 mm of ethanol depressed the mechanical activity of the ethanol treated hearts for the first 15 minutes of perfusion only (Table V) while addition of 200 mm of ethanol to control hearts resulted in a significant depression throughout the perfusion period (Table IV). It has previously been shown that a degree of alcohol adaptation might occur during chronic ethanol administration as was shown for certain enzymes.[9,20]

It has previously been suggested that both acute and chronic effects of ethanol may be related to the release of myocardial norepinephrine by acetaldehyde, the first breakdown product of ethanol.[11] This might be an additional factor in vivo since the above studies on the isolated heart indicate that ethanol per se can cause significant changes in myocardial contractility and tension development. The decreased mechanical performance may also be due to depressed ATPase activity of the contractile protein since chronic ingestion of ethanol by rats over 8 to 17 months resulted in decreased myofibrillar ATPase activity.[12] Conflicting results regarding the effects of ethanol on mechanical activity and coronary flow rate have been reported, e.g., coronary flow was reported to be unchanged,[4,35] increased,[3,26,34] or decreased by ethanol,[4] whereas the results obtained in this study indicate that while ethanol has no effect on the coronary flow rate of ethanol treated hearts (Table V) it acts as a vasodilator in the control hearts (Table IV). Our results are in agreement with earlier studies on the effect of ethanol on myocardial mechanical activity which also indicated a decline in contractility with high concentrations of ethanol.[1-3,11] On the other hand, Webb and Degerli[37] reported that low dosages of ethanol to dogs (0.5 to 1.5 Gm. per kilogram) resulted in an increase in work load, while higher dosages (5 Gm. per kilogram) resulted in rapid and progressive deterioration. In contrast to the present results, Maines and Aldinger[12] found that chronic consumption of 25 per cent ethanol by rats for 4 months resulted in a significant decrease in potential ventricular contractile force. This might be due to the higher concentration ethanol since it has been found in our experiments that ethanol concentrations exceeding 20 per cent had a deleterious effect on rats.

Summary

The effect of ethanol (100 and 200 mm.) was studied on the metabolism and function of isolated perfused rat hearts from control and ethanol treated rats.

Ethanol (200 mm.) increased incorporation of palmitate-C[14] uptake into tissue lipids while C[14]O$_2$ formation was decreased, indicating a shift from exogenous to endogenous fuel.

Long term administration of ethanol resulted in a significant change in the pattern of myocardial palmitate metabolism as shown by the increased incorporation of palmitate-C^{14} into tissue lipids

Ethanol depressed work performance and tension development of control rat hearts. Long term administration of ethanol had no effect on the work performance of the perfused rat heart but an increase in t PH was suggestive evidence of an impairment in contractility

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Relation of shunt flow and right ventricular pressure to heart valve structure in atrial septal defect

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Heart valve leaflets become focally thickened, focally thinned, and somewhat deformed with age in the absence of known or presumed endocarditis.[1-3] Accentuation of such changes under conditions of altered blood flow lends further support to the contention that these are probably attributable to long-term physical stresses associated with valve function. A variety of valvular deformities are also noted in hearts with congenital anomalies. Some are examples of unusual valve placement or valve malformation.[4] However, in malformed hearts with well-differentiated and normally situated valves, leaflet changes may be greater than expected for a given age, or may follow patterns not seen in normal hearts at any age. Although it seems reasonable to presume that many valve changes in both normal and malformed hearts represent reactions to mechanical stresses, there is little information concerning the precise relationship between specific stresses and the different types of reconstruction and degeneration seen in valve tissues. Since patients with congenital heart disease have often had cardiac catheterization studies, autopsy specimens from such cases provide an opportunity for the characterization of valve thickenings in the light of antemortem hemodynamic data. For this purpose, valves of hearts with atrial septal defect of the fossa ovalis (secundum) type were studied, and the effects of large shunts and relatively low right ventricular pressures compared with the effects of small shunts and high pressures. On the right side of the heart, where in vivo hemodynamic differences between the two groups were greatest, valve changes associated with large shunts and relatively low pressures were consistently different from those associated with small shunts and high pressures. A prominent characteristic deformity in the mitral valve was very nearly the same in

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Table I Catheterization data for hearts with atrial septal defect of fossa ovalis type

Group	Specimen No.	Age (yr.)	Sex	Pulmonary artery pressure (mm Hg)	Shunt flow (L./min.)	Stroke volume right ventricle (ml.)
Flow	1	20	F	20/10	16 73	244
	2	38	F	37/16	17 24	269
	3	48	F	41/14	13 80	259
	4	47	M	45/–	7 10	147
Pressure	5	0 3	M	60/	"Small"	—
	6	38	M	71/26	3 44	81
	7	44	M	73/26	2 03	65

Right ventricular pressure

both large shunt flow and high pressure hearts.

Materials and methods

All of the valves of 7 hearts with isolated atrial septal defect of the fossa ovalis (secundum) type from patients who had cardiac catheterization shortly before death were studied in detail. The different effects of increased chamber volume and increased pressure on the parietal endocardium of these hearts have been reported elsewhere Because the lesions of the mitral valve were so prominent this valve was studied in 45 additional hearts with atrial septal defect of these 29 had an isolated defect 3 were cases of Lutembacher's complex and 13 had atrial septal defect complicated by total anomalous pulmonary venous drainage. Twenty-seven normal hearts served as controls All of the specimens used for this study are from the research collection of the Congenital Heart Disease Research and Training Center

In 6 of the 7 cases with suitable hemodynamic data catheterization had been performed 1 week to 2 months before surgical closure of the septal defect (2 weeks to 2 months prior to death) the seventh patient had no surgery and was catheterized one week before death Catheterization data for the 7 hearts is given in Table I Relatively high shunt flows and relatively low pulmonary artery or right ventricular pressures were recorded for 4 of the patients these form the flow group Three with relatively high pressures and low shunt flows, form the pressure group. In the flow group left-to-right shunt flow ranged from 7 10 to 17.2 L per minute with a mean of 13 7 pressures ranged from 20 mm Hg systolic and 10 mm Hg diastolic to 45 systolic (right ventricular) with means of 38 mm Hg systolic and 13 mm. Hg diastolic. In the pressure group pressures ranged from 60 mm Hg systolic (right ventricular) to 73 mm. Hg systolic and 26 mm. Hg diastolic shunt flow was 2 03 to 3 44 L. per minute.

Valve circumferences were determined at the valve ring insertions using a flexible plastic ruler Valve thicknesses were measured by means of a micrometer caliper read to the nearest tenth of a millimeter Determinations were made at three locations on each leaflet (1) at the free or distal end (2) at the line of closure and (3) midway between the leaflet insertion and the distal end Since heart chambers had been opened by prosectors before the hearts were acquired and the specimens had been in 10 per cent formalin solution for several weeks to several years, an attempt was made to evaluate the consequences of different fixation periods. For this purpose, the usual series of standard measurement of chamber size and valve circumference were repeated on each heart and compared with previous measurements made within a few days of the original acquisition of the heart. No significant deviations from the original measurements were detected

Microscopic sections were prepared from at least 8 tissue blocks taken from pulmonic

and aortic valves and 4 to 6 blocks taken from tricuspid and mitral valves. Paraffin sections were cut at 7μ and stained with hematoxylin and eosin and with the Weigert–van Gieson and silver impregnation methods for connective tissue. The periodic acid–Schiff (PAS) reagent and the dialyzed iron method were used to study the localization of acid mucopolysaccharides (AMPS); sections from 2 blocks of each valve were stained with azure A and toluidine blue to show metachromatic substances, and adjacent tissue blocks were used to prepare frozen sections which were stained with Sudan IV to demonstrate fat.

Terminology. We have used the following modification of the terminology for valve leaflet anatomy proposed by Gross and Kugel. *Radial location.* The portion of the leaflet or cusp near its insertion on its fibrous ring is called either the base or proximal portion; the zone most distant from the insertion, defined by and including the line of closure and the free edge, is called the free end or distal portion; the intervening zone, between the proximal and distal portions, is called the body or mid portion. *Tissue layers.* The deep dense collagenous layer normally prominent in the proximal portions is referred to as the *fibrosa*; the looser connective tissue zones are called the *spongiosa*; the superficial layers are named for the chambers which face the leaflet or cusp surfaces when the valve is closed, i.e., *atrialis* and *ventricularis* for the atrioventricular valves and *ventricularis* and *arterialis* for the semilunar valves. The terms *proximalis* and *distalis* have been used by others to designate valve surfaces with respect to the direction of blood flow; these terms have been avoided in the present report to prevent confusion with the terms used for radial location.

Results

Thickening and architectural modifications in excess of expected changes for any given age were discernible in tricuspid, pulmonic, and mitral valves of all 7 hearts with isolated atrial septal defect (ASD). Aortic valves resembled those of normal hearts of the same age; the cusps were if anything somewhat thinner than usual. All of the valves were anatomically competent and patent. Tricuspid and pulmonic



Fig. 1. Typical tricuspid and pulmonic valves of hearts with atrial septal defect of the fossa ovalis type. A, Tricuspid leaflets are markedly and irregularly thickened from the base to the free edge in a heart with high shunt flow and relatively low right ventricular pressure (Patient 2); chordae are thickened and the anterior leaflet is more affected than the others. B, In a heart with high pressure and relatively low shunt flow (Patient 6) the leaflets are thickened mainly from the lines of closure to the free edges; the leaflets are uniformly involved. C, Pulmonic cusps of a heart with high shunt flow (Patient 2) have enlarged and flattened nodules of Morgagni (arrow) and are thickened at the base. D, Pulmonic cusps in a heart with high pressure (Patient 7) have excessively sharp and prominent nodules (arrow) but are otherwise thin and delicate.

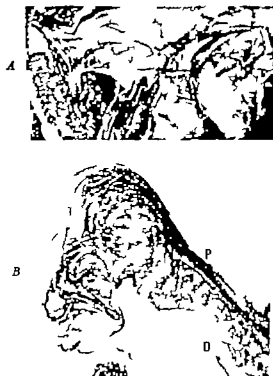


Fig 2 Typical mitral change from a heart with atrial septal defect of the fossa ovalis type. *A* Gross appearance (Patient 6) The valve is prominently thickened about the posterior commissure. Both the leaflets and the chordae are involved (arrow) The lesion was somewhat more prominent in the hearts with high shunt flow *B* Microscopic appearance (Patient 2). *P* = Atrial aspect, *D* = ventricular aspect. Fibroelastosis of the atrialis is a prominent feature. In the distal portion, a marked increase of loose connective tissue in both atrialis and ventricularis and the enlarged spongiosa convert the valve tissue into a characteristically structured large fibroelastic mass. (Weigert–van Gieson stain. ×15)

valve changes associated with large interatrial shunts and relatively low right ventricular or pulmonary artery pressures were easily distinguishable from those associated with high right-sided pressures and relatively small shunts. In general marked extensive thickenings were associated with high shunt flow while moderate thickenings localized to the line of closure were characteristic of elevated right ventricular pressure. Mitral valve changes were striking and characteristic but similar for both flow and pressure groups.

Alterations in the tricuspid, pulmonic and mitral valves will be described in detail. Photographs of typical valves from the series of hearts with ASD are presented in Figs. 1 and 2 photomicrographs are presented in Figs. 3 to 5 Significant valve findings in normal and abnormal hearts are summarized and compared semidiagrammatically in Fig 6

Tricuspid valve

FLOW GROUP Tricuspid leaflets were enlarged in proportion to the dilatation of the tricuspid valve ring and extensively thickened The mean thickness of anterior leaflets was 1 4 mm at the distal end and 0 6 mm in the midportion compared to corresponding values of 0 8 and 0.3 mm. for the normal hearts (A typical valve is shown in Fig 1 *A*) Thickenings were especially prominent about the insertions of the chordae tendineae, forming prominent longitudinal ridges on the ventricular surfaces of the valve leaflets extensions of second and third order chordae could often be traced all the way to the tricuspid ring on the medial and posterior leaflets. The chordae themselves were markedly thickened particularly in relation to the anterior leaflet focal adhesions between adjacent structures were present. On the atrial surfaces of the leaflets, irregular indistinctly circumscribed fibrous nodules corresponded to the chordal prominences of the ventricular surfaces. These were most evident at the line of closure and in the distal portions of anterior leaflets, where associated Lamblian excrescences were occasionally noted Nodular changes were least evident in medial leaflets. Small calcified foci were sometimes evident on the ventricular surface of the anterior and posterior leaflets adjacent to the annulus fibrosus. Microscopically (Fig 3 *A* and *B*) dense homogeneous and relatively acellular collagen was prominent in the annulus fibrosus and in the fibrosa layer Layered fibroelastic thickening was marked in the atrialis layer forming prominent ridges at the line of closure fibroelastic thickening of the ventricularis was present only in the distal portions of the leaflets. The spongiosa showed considerable fibroelastosis in the proximal portions but relatively little in distal zones there were also foci of connective tissue containing many fibroblasts. The fibrous tissue of the annulus and the fibrosa stained intensely with PAS stains for acid mucopolysaccharides and lipid re-

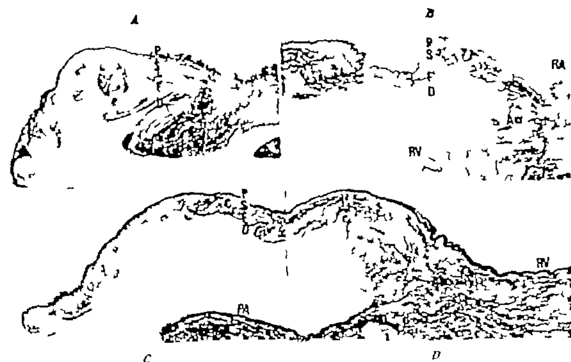


Fig 3 Sections of tricuspid and pulmonic valves from hearts with atrial septal defect of the fossa ovalis type with high shunt flow and relatively low right ventricular pressure (flow group). *A* Distal portion of tricuspid leaflet (Patient 2). *B* Proximal portion of tricuspid leaflet (Patient 4). C Pulmonic cusp (Patient 2). Note the thickened collagen bundles in the fibrosa (*F*) at the insertion of the chordae and in the proximal portion of the tricuspid. There is also fibrosis in the thickened ventricularis (*P*) and fibroelastosis in the atrialis (*D*) in the distal portion; the spongiosa (*S*) is thicker than normal in the distal portion. In the pulmonic cusp the fibrosa (*F*) is thickened and the associated spongiosa (*S*) largely replaced by fibroelastosis and collagenous tissue. *Ao* = Annulus fibrosus *PA* = pulmonary trunk, *RA* = right atrium *RV* = right ventricle. (Weigert-van Gieson stain, ×20)

vealed greater than normal deposition of these materials in the annulus, the distal portion of the fibrosa and the ground substance of the spongiosa.

PRESSURE GROUP Tricuspid leaflets were enlarged and somewhat redundant for the enlarged tricuspid orifice. In contrast to the findings in the flow group the bodies of the tricuspid leaflets in the pressure group were only slightly thickened compared to those of the normal subjects (Figs. 1 *B* and 6) Changes were relatively uniform from leaflet to leaflet, and thickening was limited to the distal portions average thickness at the distal end was 1 4 mm compared with 0.8 for the normal group. The most prominent thickenings were at the lines of closure where leaflets were also roughened by occasional Lambllan excrescences There was only minimal focal fusion of first order chordae near the points of insertion at the anatomical edges of the anterior leaflets. Chordal extensions were only slightly accentuated and only in the distal halves of the leaflets. Microscopically (Fig 4 *A* and *B*) the spongiosa was widened in the distal portions. A fibroelastic mound was present in the atrialis layer at the line of closure the ventricularis was not involved The annulus fibrosus and the fibrosa showed very little fibrosis.

Pulmonic valve

FLOW GROUP Pulmonic cusps in this group were definitely thickened but relatively somewhat less than the tricuspid leaflets of the same heart (Figs. 1 *C* and 6) Distal zones were 0 9 mm. thick on the average compared with the normal value of 0 6 mm. cusp bodies were an average of 0.3 mm thick (normal 0 2) The bases of the cusps were irregularly roughened by prominent, firm transverse ridges on their

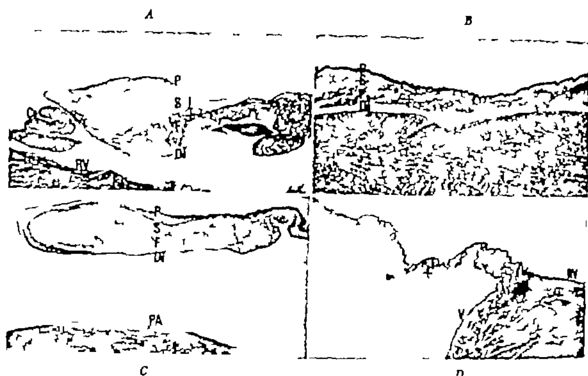


Fig. 4. Microscopic appearance of typical tricuspid and pulmonic valves from hearts with atrial septal defect of the fossa ovalis type with high right ventricular pressure and relatively low shunt flow (pressure group). *A*, Distal tricuspid (Patient 7). *B*, Proximal tricuspid (Patient 7). *C*, Distal pulmonic (Patient 7). *D*, Proximal pulmonic (Patient 6). The spongiosa (*S*) is greatly widened in the distal portions of both valves, while there is only slight thickening of the fibrosa (*F*) in the proximal portion of the tricuspid leaflet. The proximal pulmonic cusp is nearly normal. D_I = Ventricularis of tricuspid leaflet and arterialis aspect of pulmonic cusp. *Ct* = chorda. *PA* = pulmonary trunk. *P* = atrialis of tricuspid leaflets and ventricularis of pulmonic cusp. *RV* = right ventricle. *V* = sinus of Valsalva. (Weigert-van Gieson stain. ×20.)

ventricular surfaces. The ridges were most evident near the commissures. Commissural zones at the valve ring were somewhat thickened and commissural demarcation focally obliterated. In contrast commissural zones showed separation above the valve ring especially in the left anterior location. Broad little hillocks were evident in the pulmonary trunk over the apices of the commissures; these were most prominent over the posterior commissures and least prominent over the left anterior commissure. The noduli Morgagni thicker and wider than normal projected prominently from the distal cusp edges obscuring the line of closure on the ventricular side. This change was greatest in the left posterior cusp and least in the anterior cusp. There were no fenestrations and Lambl̈an excrescences were found in only 2 of the 4 cases. Near the distal edge transverse fibrous ridges extended from commissure to commissure on the arterial surface. Nodules, often confluent with the noduli Morgagni were present at the distal ends of the right and left posterior cusps. The proximal segment of the pulmonary trunk seemed dilated. Occasional calcific intimal thickenings in the sinuses of Valsalva were most numerous in the right and left posterior sinuses. Microscopically (Fig. 3 C) the striking commissural changes corresponded in each instance to longitudinal collagenous columns extending from a thickened fibrosa to the pulmonary trunk with prominent subendothelial fibroelastosis at the lower portions. *Other changes* were similar to those described for the tricuspid leaflets in the flow group.

PRESSURE GROUP. Thickening of pulmonic cusps in these hearts was *limited* to the line of closure and to the noduli Morgagni on the ventricular surface (Figs. 1 *D* and 6). At the distal end thicknesses averaged 0.9 mm (0.6 for the normal group) while for the body the average was *only* 0.1 mm.

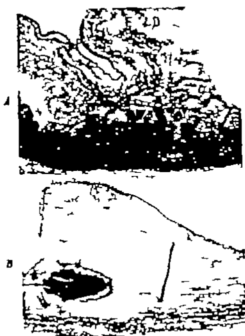


Fig 5 Microscopic appearance at the commissure of pulmonary valve of heart with atrial septal defect of the fossa ovalis type. *A* The lower portion of commissure from heart (Patient 2) with high shunt flow and relatively low pressure (flow group) show fibroelastosis of the spongiosa (*S*) and thickening of the fibrosa (*F*). (Weigert–van Gieson stain ×20.) *B*, The upper portion of a commissure from a heart (Patient 7) with high right ventricular pressure and relatively low shunt flow (pressure group) (Patient 7) has prominent fibrous ridge with focus of calcification (arrow) Darker areas are zones of increased staining for acid mucopolysaccharides. (Hale stain [Abul-Haj modification]. ×20)

(less than the normal value of 0 2) Sharply demarcated nodules were present in the distal central portion of each cusp however laterally the anatomical edges were thinned and in all of the cases, fenestrated Lamblian excrescences were not present. The body of each cusp was delicate. At the base of the cusps thickenings were much less than those seen in the flow group Changes about the commissures were also quite different the inferior commissural zones were neither thickened nor obliterated and the upper portions were not separated. Instead sharply demarcated narrow longitudinal ridges extended up to prominent, narrow hillocks in the pulmonary trunk over the commissural apices. The supravalvular segments of the pulmonary trunks were somewhat dilated but intimal thickenings in the supravalvular sinuses were fewer and smaller than in the flow group Sharply circumscribed collagenous elevations contained accumulations of stainable acid mucopolysaccharides and focal calcifications at the upper aspects of the commissures. The lower commissural zones were similar in architecture to those in the flow group but less involved Microscopically (Figs. 4 C and D) other changes were similar to those seen in tricuspid valves of the pressure group but were less marked

Mitral valve

HEARTS WITH CATHETERIZATION DATA In all 7 of the cases of isolated ASD with catheterization characteristic firm and rigid thickenings deformed the posterior halves of the anterior and posterior mitral leaflets (Figs. 2 and 7) These changes were only slightly more prominent in the flow group The greatest thickenings were in the posterior portions of the anterior leaflets, where the average thickness was 2 0 mm compared with 1 2 mm for normal mitral leaflets at the same location. The lesions were easily appreciated on both atrial and ventricular aspects. The atrial surfaces were roughened and the ventricular surfaces had prominently widened chordal insertions extending onto the leaflets to form prominent ridges. Chordae tendineae near the posterior commissure were markedly thickened and focally adherent anterior chordae were less involved. Lamblian excrescences were occasionally seen where leaflets were most involved. Microscopically (Fig 2) the leaflets were similar in the flow and pressure groups. All the valve tissue layers were thickened and in some places, poorly demarcated The distal ends of the leaflets were transformed into whorled masses of elastin and collagen fibers. At the line of closure, the marked thickening of the atrialis consisted of fibroelastic layers. The spongiosa and fibrosa at the distal ends contained much stainable acid mucopolysaccharide as well as foci of adipose tissue.

SUPPLEMENTARY HEARTS WITH ASD Examination of the 45 additional hearts with ASD revealed the characteristic mitral deformity in 26 The distribution of the deformity according to congenital heart

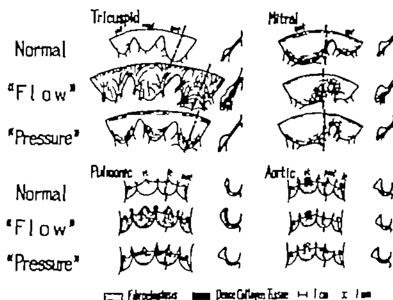


Fig. 6 Semidiagrammatic comparison of gross and microscopic appearances of normal heart valves with those in atrial septal defect of the fossa ovalis type. *"Flow"* = ASD with high shunt flow and relatively low right ventricular pressure. *"Pressure"* = ASD with high right ventricular pressure and relatively low shunt flow. The interrupted lines on the leaflets and cusps indicate the positions at which cross-sections are represented. All of the valves have been drawn to the same scale. (Calibration: 1 cm. line is for opened valves; 1 mm. line is for cross-sections.)

disease complex is given in Table II. Twenty-one of the additional hearts were samples of isolated atrial septal defect of the fossa ovalis or proximal type; of these 17 had the typical mitral change. If the 7 hearts with catheterization data which form the basis of this report are included, 28 of the 31 cases (90 per cent) of isolated ASD (fossa ovalis or proximal type) had the typical mitral lesion. The 3 hearts that did not were from infants less than 8 days old at death; the valves with lesions were from hearts of individuals whose age at death ranged from 35 days to 72 years. Three of the supplementary cases had ASD of the proximal (sinus venosus) type; all of the specimens had the typical mitral lesion; all were older than 8 years. Among all the cases with the lesions, the degree of the mitral valve change definitely increased with age.

Five of the supplementary hearts had ASD of the primum type; 4 of these had a deep cleft in the anterior leaflet of the mitral valve and did not have the posterior commissural lesion. The fifth, with a very small partial cleft, had the typical mitral change.

Only 2 of the 13 cases of total anomalous pulmonary venous drainage with ASD had the typical mitral valve lesion; both of these had relatively large mitral orifices, while the mitral orifices of the 11 cases without the mitral lesion were normal or smaller than expected for their respective ages. All 13 hearts in this group were from individuals who were older than 23 days.

Two of the 3 patients with ASD and mitral stenosis (Lutembacher's complex) who were older than 13 years of age had extensive mitral thickening. The configuration of the valves differed somewhat from that seen in the 7 hearts that form the basis of this report; the thickest zones were nevertheless about the posterior commissures.

Discussion

Valvular thickenings associated with ASD, including characteristic mitral lesions similar to those described in this report, were presumed to be the consequence of previous endocarditis in early case reports.[7,8] The incidence of rheumatic valvulitis is said to be greater in hearts with congenital anomalies than in otherwise normal hearts.[9] Instances of severe mitral stenosis with ASD are numerous[10,11] and

Table II Incidence of typical mitral deformity in 52 hearts with ASD

Anomalous complex	*No. available*	*Mitral deformity*		*Remarks*
		Present	*Absent*	
Isolated ASD Fossa ovalis type*	28	25	3	Valves with deformity from patients 35 days to 72 yr old without deformity less than 8 days
Proximal type	3	3	0	All patients 8 yr or older
Primum type, with clefted anterior mitral leaflets	5	1	4	Valve with deformity only slightly clefted all patients older than 1 mo.
Lutembacher' complex (ASD with mitral stenosis)	3	2	1	Mitral deformity imposed on other valve changes all patients 13 yr or older
ASD with total anomalous pulmonary venous drainage	13	2	11	All patients older than 23 days

*Includes the 7 hearts with catheterization data.

some are convincingly of rheumatic origin.[21] Rheumatic lesions are however characteristically nodular markedly deforming and functionally destructive vascularized scarifications,[22] quite different from the relatively uniform and orderly proliferative and degenerative changes seen in our cases. In none of the seven hearts with ASD and antemortem hemodynamic data which form the basis of this report were there any diagnostic or presumptive microscopic epicardial or myocardial evidences of rheumatic heart disease or any recorded clinical episodes to suggest rheumatic fever None of the lesions of either the right-sided or mitral valves showed any evidence of fresh or recent thrombus formation or any conclusive evidence of thrombus organization. Roesler[11] who reported that 77% of his cases with ASD had tricuspid and mitral thickenings, attributed the tricuspid changes to the increased right-sided blood flow but did not offer a hemodynamic explanation for the mitral lesion.

In the present study of hearts with ASD differences in the distribution and composition of valvular thickenings corresponded to in vivo hemodynamic differences. High shunt flow and relatively low right ventricular pressure were associated with extensive fibrosis and fibroelastosis of tricuspid and pulmonic valves high right ventricular pressure and relatively low shunt flow were associated with much less thickening and changes were clearly predominant about the lines of closure In both instances, leaflet architecture was generally conserved and there were gradual transitions between normal and thickened portions. The characteristic rigid fibroelastic deformity about the posterior commissures of the mitral valves was present when otherwise normally formed mitral valves were associated with predominant left to-right shunt it was unusual in hearts with mainly right to-left atrial shunt. The degree of the mitral change was not related to the level of right ventricular pressure or to the degree of atrial shunt flow It was not seen in hearts of patients less than 1 month old but when the deformity was present, its severity was greater with increasing age. Our findings support the contentions that (1) The tricuspid pulmonic, and mitral lesions described in this report, and many of the valvular changes noted by others in ASD are acquired but are not of rheumatic or thrombotic origin (2) they do not form part of the initial anomalous complex and (3) both the right-sided and mitral valve changes are mainly reactions to hemodynamic mo-

chanical stresses associated with ASD. The apparently proportional increase in the area of valve tissue corresponding to the dilated right-sided orifices provides additional evidence that the changes are part of a long term adaptive response.[14]

Many authors have attributed heart valve changes to hemodynamic stresses, applying such terms as "valvular hypertrophy"[4] and "central hypertrophy"[17] to nonspecific thickenings of the spongiosa with preservation of normal layering and without increased vascularity or cellularity. Subendothelial fibrotic "aging" changes in valves and chordae tendineae of otherwise normal hearts have been interpreted as reflecting the long term effects of normally present hemodynamic stresses.[1,2,4,15,29] Elastic hypertrophy of the proximalis has been attributed to irritation of blood flow, while plaque formation at the line of closure, fibroelastosis of the spongiosa, and sclerosis of the fibrosa have been attributed to stretching tensions and compression accompanying the incessant opening and closing of the valves. Thickenings at the line of closure have been described. These have been called "sclerosis marginalis nodularis valvularum" and sometimes contain a fatty component[8] distinguishable from atherosclerosis.[29] Since the valve changes in our cases with ASD were probably related to altered mechanical stresses, a speculative consideration of the findings in the light of the catheterization data may be instructive.

During cardiac cycle, heart valves are subjected to stretching and compressive forces as pressures and chamber configurations change and to frictional and vibrational forces as blood flows through the valve orifices. The chordae tendineae, valve leaflet, and annulus fibrosus of each atrioventricular valve may be considered to form a continuous, relatively inextensible mechanical system (valve system) which develops tension in response to the stretching forces. In Fig. 7, the changes in configuration of the tricuspid valve system during the cardiac cycle are represented diagrammatically for normal hearts and for hearts with ASD. The inferior and anterior papillary muscles, and their associated chordal and leaflet tissues, are shown

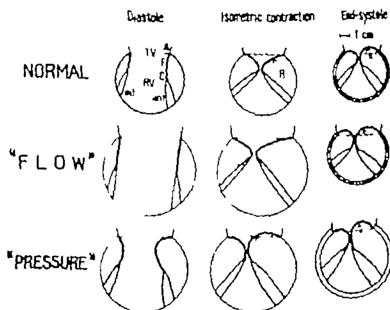


Fig. 7. Diagrammatic comparison of the configuration of the tricuspid valve system of normal hearts with those having an atrial septal defect of the fossa ovalis type during the phases of the cardiac cycle. The valve system consists of papillary muscle (*inf* = inferior, *ant* = anterior), chordae tendineae (*C*), leaflet (*F*), and annulus fibrosus (*A*). The right ventricular chamber is represented as a section through a sphere with a segment missing at the tricuspid orifice (*TV*). Attention is directed to the changes in radius of curvature (*R*) of the leaflet. Further explanation in text.

within a circle representing the right ventricular chamber. During diastolic filling of a normal ventricle the myocardium is relaxed, the pressure is low, and tension in the tricuspid valve system is minimal. During isovolumetric contraction with the valve closed and myocardial tension and chamber pressure increasing, the shape of the chamber and the configuration of the valve system remains relatively constant; tension in the valve system parallels the tension in the myocardium and compressive forces at the coapted distal portions of the leaflets increase. During ejection, ventricular mural curvature increases as chamber volume decreases. The valve system can neither lengthen nor shorten so that the leaflets "bulge" or "bow," resulting in a decrease in their effective radius of curvature. Since the tension developed in a leaflet is proportional to its radius of curvature (Law of La Place), forces tending to stretch the leaflets should decrease during ejection even though intraventricular pressure is still high. The tension in the leaflets is probably greatest as ejection begins. Thus, for normal hearts, tension in the tricuspid valve system is very low during diastole when pressure is nearly zero, increases with increasing pressure during the isovolumetric phase of systole, and then decreases in the leaflets during ejection as leaflet radii of curvature decrease, even while pressure is elevated.

In the flow group (ASD with large shunt and relatively low pressure) right ventricular chambers were larger than those of the pressure group (high pressure, small shunt) and much larger than those of normal control subjects. This was probably associated with greater than normal stretching of the valve system. During isovolumetric contraction of the markedly enlarged ventricle, the adequate leaflets closed over the large orifice and their radii of curvature were greater than those of either normal or pressure group hearts, resulting in high leaflet tensions. During ejection, leaflet curvature in the flow group probably reached nearly normal values, but since pressure was only moderately elevated, tension was probably only slightly greater than normal. The area of apposition at the distal ends of the leaflets was probably not excessive and the pressure compressing the coapted zones was only moderate. Thus the major factor in the elevation of tricuspid valve system tension in the flow group was ventricular enlargement rather than pressure elevation and valve system tensions were probably close to mean or maximum values during most of the isovolumetric period. In the pressure group hearts, pressure in the less dilated ventricles reached very high levels during isometric contraction, but leaflet radii of curvature were probably normal or less than normal as the somewhat redundant valve leaflets bowed, so that stretching tensions probably approached normal values. At the end of systole, the radius of leaflet curvature was probably much smaller than in normal or flow group hearts. Although the rate of increase of pressure and tension was greater in the pressure group, the very high pressures prevailed for a relatively short time and in relation to leaflets with relatively small radii of curvature. However, the high pressures compressed the extended coapted zones more than in the flow group.

In the flow group, the marked oriented and fairly uniform sclerosis of the fibrosa, extending continuously from the annulus fibrosus through the leaflet bodies into the chordae tendineae, corresponds to the markedly elevated stretching tension distributed more or less uniformly through the valve system during both systole and diastole. In the pressure group, the slight to moderate fibrosis of fibrosa and chordae corresponds to the relatively lower mean stretching tension throughout the cardiac cycle; the sharply demarcated augmentation and fibrosis of the spongiosa in the distal portion corresponds to the marked compression of the enlarged coapted zones by the high ventricular pressure. The focal accentuation of thickening in the chordae to the anterior leaflet in the flow group was probably related to the fact that, though the anterior leaflet is the largest of the tricuspid leaflets, its chordae tendineae are fewer in number than those inserting on each of the other tricuspid leaflets. Since the total tension on any chordal leaflet combination is divided among its chordae, the tension in each of the anterior leaflet chordae may be expected to be greater than the tension in each of the more numerous

chordae to the other leaflets. The absence of focal accentuations of chordal thickening in the pressure group is probably related to the presence of the tight leaflet coaptation when tension is maximal the large coapted zone may function as a fibrous ring distributing tensions uniformly among all the tricuspid chordae insertions.

Hypercellularity and ground substance changes at the line of closure were greatest in the pressure group despite the fact that over all valve thickening was less than that seen in the flow group Such thickenings were fairly uniform in all 3 leaflets and may be attributed to the action of deforming stresses due to mutual impact of the leaflets Such stresses are a function of the momentum of the valve leaflets at the time of closure and would be expected to act mainly at and near the lines of closure Since momentum at the time of impact is proportional to the relative velocities of the leaflets, changes related to impact should be greatest in the hearts with the most rapidly increasing ventricular pressures i e those of the pressure group In the flow group impact forces are probably reduced because the elevated atrial inflow from the large shunt reduced leaflet velocity by increasing resistance to valve closure Also in flow hearts the relatively rapid flow from right atrium to right ventricle during diastole probably results in lower than normal lateral pressure on the opened leaflets. Leaflets should therefore drift nearer their closed positions by the onset of systole Leaflet velocity at impact would then be relatively low because of the shortened traveling distance between open and closed positions.

Although the distribution of the stresses related to stretching and compression correspond closely to the distribution of fibrosis in the annulus fibrosus and chordae turbulence of flow and boundary shearing effects probably also play a role[33,34] Augmented flow through the tricuspid valve ring may result in greater than normal turbulence and associated increased frictional effects and vibration of the valve system Reynolds[35] number for blood flow through such an orifice is not known and it is unlikely that the usually stated critical value of 2 000 based on the steady flow of water through straight tubes, can be used in any simple manner to predict the degree of turbulence with respect to other configurations, such as valve orifices.[22] In any case turbulence about the tricuspid orifice would be greatest in the flow group and could modify the architecture of the leaflets by local pressure reduction frictional effects, or vibrations transmitted to the bodies of the leaflets. Shearing forces due to drag between adjacent tissue layers of unequal deformability would also be greatest where flow rates are greatest, i.e., in the flow group and at the interfaces between the spongiosa and the fibrosa. The atrial side of the tricuspid valve leaflets and the ventricular side of the pulmonic cusps should be more exposed to the effects of high flow than the other surfaces. Indeed, the most prominent fibroelastosis by far was present in the tricuspid valve atrialis and the pulmonic valve ventricularis of the flow group (Fig 6) indicating that this proliferation is probably related to the increased flow

Other pulmonic valve differences can be explained in terms of presumed differences in valve tensions The pulmonic orifices were largest in the flow group leaflet radii of curvature and valve tensions were therefore probably greatest in these hearts. The cusps in this group were greatly thickened by dense collagen especially about the commissures and at the base i.e. near the junction of the leaflets with the annulus. The left posterior cusp was more thickened than the others. Attached at the interventricular septum this cusp was probably the most firmly fixed and perhaps subjected to relatively greater tensile vibratory and shear effects than the others The posterior commissure, located on the septum was thicker but less separated than the others. The greater separation of the nonseptal commissures is probably associated with the greater dilatation of the less firmly anchored nonseptal portion of the valve ring The prominent noduli Morgagni on the arterialis side of all the pulmonic cusps is probably related to impact at valve closure. Extension of the enlarged nodulus toward the ventricularis on the anterior cusp could be related to the right ventricular outflow pattern. The curvature of the outflow tract is such as to direct much of the flow toward the anterior cusp. This

may result in a slight delay in the closing of the anterior cusp so that it strikes the left and right cusps after they are very near their closed positions. This effect would be especially evident under conditions of increased flow in the flow group. In the pressure group the less dilated ventricle corresponded to a less dilated valve orifice and practically no separation of the commissures. The markedly elevated pulmonic pressure during diastole accounts for the characteristic thickening of the commissures and the accentuation of the noduli and spongiosa of the coapted portions.

Although differences in right ventricular flow and pressure appear to correspond to differences in architecture of the right-sided valves, it should be recalled that patients with ASD who develop pulmonary hypertension have usually had a period of relatively high shunt flow and low pressure. Structural changes of high pressure would therefore be expected to be superimposed on thickenings which developed during the high flow phase in the hearts of the pressure group. To some extent this was true, for there was nearly always some diffuse fibrous thickening of leaflets in the pressure group. The fact that such thickenings were much less extensive than those seen in the flow group suggests that the changes may regress when the hemodynamic conditions change, or that chambers of hearts in the pressure group did not reach the size of those in the flow group.

The mitral lesions, so prominent about the posterior commissures in hearts with marked left-to-right shunt, can also be related to associated hemodynamic conditions. In addition to the direction of transseptal flow the relevant factors are probably the enlarged right ventricle, the position of the septal defect, and the reduced atrioventricular flow in the presence of a nearly normal mitral orifice.[11] The posterior commissure is located over the interventricular septum, i.e. the wall common to both ventricles. Because the right ventricle is greatly enlarged in ASD the septal surface of the left ventricle is disproportionately larger than the surface of the free wall. As a result the posterior commissure is more widely opened than the anterior commissure. In addition the supravalvular edge of the remaining atrial septum probably diverts a stream of atrioventricular flow toward the posterior commissure. This increased local flow probably elicits the focal fibroelastic response. The absence of the lesion in most hearts with ASD and total anomalous pulmonary venous drainage supports this contention by indicating that the direction of transseptal flow must be mainly left to right for the development of the mitral lesion; flow directed toward the posterior commissure would hardly be expected with shunting from right to left. The accentuated distal component of the mitral thickening may in part also be related to compressive stresses acting during impact. Since the mitral leaflets with the lesion were functionally competent and related to orifices of normal size the zone of leaflet apposition was probably normal or greater than normal. Indeed the leaflets seemed redundant rather than retracted. The relatively low atrial resistance to mitral valve closure due to left-to-right atrial shunting probably resulted in increased leaflet momentum and impact at closing particularly when atrial shunting was large. Phonocardiographic evidence supports this suggestion.[23,24] Incompetent mitral valves would not provide these hemodynamic conditions; indeed deeply clefted mitral valves associated with ASD did not show the typical change.

Since mitral valvular fibrosis ranged from slight in young hearts to marked in older individuals, we suggest that some of the mitral changes in Lutembacher's complex, especially in older patients, are secondary to the altered flow patterns associated with atrial septal defects. If mitral orifices are stenotic from the onset in hearts with ASD the characteristic changes may well occur sooner and result in typical Lutembacher's complex.[10,11,21,22]

The detailed physical explanations offered for the characteristic changes in the tricuspid, pulmonic, and mitral valves in ASD are necessarily hypothetical since they are based on presumptions regarding the distribution of mechanical forces in functioning valves. Nevertheless, we feel that such speculations are justified when a consistent pattern of change corresponds to known hemodynamic differences. observations suggest that

of endocardial and valvular lesions in the light of in vivo hemodynamic data may provide insight into the nature of connective tissue reaction to mechanical stresses. Such studies may also help to establish criteria for a more precise separation of primary from secondary anatomical changes in cardiovascular disease.

Summary

In hearts with atrial septal defect of the fossa ovalis type antemortem catheterization data corresponded to consistent differences in both the distribution and composition of tricuspid and pulmonic valve thickenings. High shunt flows and relatively low right ventricular pressures corresponded to extensive confluent fibrosis of the tricuspid chordae tendineae leaflets and annulus fibrosus, probably due to markedly elevated stretching tensions and to fibroelastosis of the atrialis probably due to increased flow High ventricular pressures and relatively small shunts corresponded to characteristic sclerosis about the line of closure related to increased compression of the coapted portions of the leaflets. Pulmonic cusps showed similar distinctive changes attributable to differences in pressure and flow A striking deformity about the posterior commissure of the mitral valve was characteristic of various types of atrial septal defect, providing the valve was generally intact and the shunt was predominantly left to right the degree of the change increased with age and is probably a consequence of disproportionate enlargement of the septal wall of the left ventricle and modification of atrioventricular flow by the atrial septal defect. There was no evidence that either the right-sided or mitral valve changes were due to previous endocarditis or thrombosis. The findings indicate that the valve changes described represent secondary proliferative and degenerative responses to mechanical stresses resulting from altered flow patterns associated with atrial septal defect.

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Observations concerning the validity of the ventricular gradient concept

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The spatial QRS-T area or ventricular gradient is one of the fundamental quantities in electrocardiography.[1] Theoretic considerations indicate it should be independent of activation sequence and permit T wave changes due to altered intrinsic properties of ventricular recovery to be distinguished from those secondary to activation order. In qualitative or semiquantitative form the gradient concept that QRS-T area is independent of activation order is frequently used in diagnostic electrocardiography. For example T wave inversion during an ectopic ventricular beat or in association with intraventricular conduction disorders is not considered to have the same diagnostic significance as an inverted T wave following normal activation. Quantitative studies have shown the QRS-T area to be imperfectly independent of activation order however and to have a wide range of normal variability which limits its diagnostic value.[1]

This report describes observations which help define conditions under which the QRS-T area is independent of activation order. They suggest that under appropriate conditions this area may be independent of activation sequence in single leads and that the gradient concept may be applied to these individual leads.

Materials and methods

There are infrequent opportunities for detailed electrocardiographic study of multiple activation patterns in the same human heart under conditions which provide reasonable assurance that other relevant factors are constant. These factors include heart rate, body and electrode positions, and intrinsic recovery properties of the heart. Such an opportunity was provided by a patient with intermittent left bundle branch block in which normal and abnormal complexes were occurring with nearly equal frequency and with equal cycle lengths. The patient was an 81 year-old woman with atherosclerotic heart disease manifest

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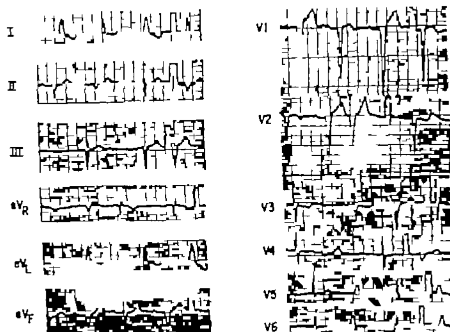


Fig. 1 Routine ECG of the patient studied. QRS complexes of normal duration and complexes evidencing left bundle branch block are evident in most of the leads shown.

by angina pectoris and congestive heart failure in addition to the electrocardiographic abnormalities. The routine 12 lead electrocardiogram is shown in Fig 1

More detailed electrocardiographic study was carried out by recording 12 bipolar chest leads at the level of the fourth intercostal space near the sternum. Anatomic lead axes were separated by 15 degrees with axes crossing at the center of the chest with 0 degrees at the left midaxillary line and 90 degrees at the midsternal line. Electrode sites were determined by the angular separation and actual distance between electrodes varied Electrode sites were located with the aid of a large protractor constructed for this purpose. Leads were recorded at a paper speed of 100 cm per second using a 6 channel recording system. Two sets of 6 and one set of 2 simultaneous leads were recorded with one lead common to all sets. Each recorded lead contained complexes with normal intraventricular conduction and ones evidencing left bundle branch block. An example of records obtained is shown in Fig 2.

QRS and ST T areas were separately measured by planimetry in each lead and values plotted against the angular positions of the lead axes. Sine waves were superimposed on these plots by placing the zero point of the sine wave on the zero value of the plots based on area. The peak amplitude of the sine wave located 90 degrees from the zero point was given an amplitude equal to the peak value of the plot based on ECG area on which the sine wave was being superimposed The total QRS-T areas during normal and abnormal conduction were also plotted as functions of angular lead axis and placed on the same graph for comparison. Data were plotted over 360 degrees so a complete sine wave could be superimposed although with the bipolar leads used the data from 180 to 360 degrees is a repetition of that from 0 to 180 degrees. Similar plots of angular lead axis versus potential have been employed by Nelson.

Results

The methods of recording and analysis used in this study were chosen to detect deviation of electrocardiographic effects from those which would be expected from a single dipolar source of cardiac electrical events centrally located in a homogeneous

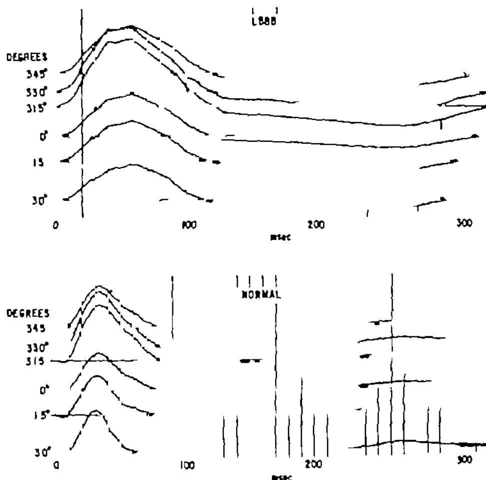


Fig Records from some of the electrode sites used in this study during normal conduction and left bundle branch block.

circular conducting medium Such a source and conducting medium would yield sine wave plots of potential versus angular lead axis. Deviation of plots from sine waves could be the result of an eccentric cardiac source nonhomogeneous conductive properties of the body multipolar cardiac electrical events, and other factors. This study was not designed to separate the influence of these individual factors and for convenience in the description of results, deviation of the plots from sine waves will be referred to as evidence of eccentricity The term will be used in a special sense to indicate that an eccentric source could account for a given finding rather than that it necessarily was the factor responsible for deviation of the plots from sine waves.

Plots of QRS-T area during normal and abnormal activation are shown in Fig 3 The difference between these varies in different leads and is least marked in those with axes of 45 60 and 75 degrees. Plots of the separate QRS and ST T areas are shown in Fig 4 QRS areas during normal and abnormal activation differ in absolute magnitude but the plots are remarkably alike in form and both correspond most closely to the superimposed sine waves at lead axes 45 60 and 75 degrees. Plots of T waves associated with normal and abnormal activation differ from each other with that of normal activation corresponding roughly to a sine wave in all leads and that of abnormal activation matching the sine wave most closely in leads at 45 60 and 75 degrees

Discussion

The patterns of total QRS-T areas versus lead axis during normal and abnormal activation were clearly related The absolute

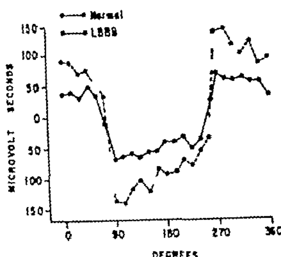


Fig. 3. QRS-T area in microvolt seconds plotted against the angular position of leads in which area was measured. The values during normal intraventricular conduction and during left bundle branch block are most nearly alike in leads with axes of 45, 60, and 75 degrees and repeated in those with axes of 225, 240, and 255 degrees.

value of the difference between areas associated with the two activation patterns was variable, however, and was smallest in leads with the least marked eccentricity. These findings indicate that eccentricity and/or other factors with similar effects on lead performance modify the applicability of the gradient concept. More specifically, they suggest that different degrees of eccentricity of cardiac events responsible for QRS and T deflections result in different ECG expressions of these events. The gradient concept requires that events during activation and recovery have equal opportunities for influencing the ECG. If events during one of these processes are more eccentric than those during the other, the electrocardiographic effects of the former will be subject to greater distortion. If a different degree of distortion occurs with another activation pattern, the QRS-T area associated with the two activation patterns will differ. In the present observations the eccentricity of events during the two activation patterns was remarkably similar. Eccentricity of events during the two recovery patterns differed with that associated with abnormal activation being greater. Similar degrees of eccentricity during the two activation patterns combined with different degrees of eccentricity during recovery to yield expressions of QRS and T which were distorted to varying degrees and to varying values of the QRS-T area. When QRS and T plots of area versus angular lead axis corresponded most closely to sine waves and thus to each other, the QRS-T areas for the two activation patterns were most nearly alike. These findings suggest that the gradient concept is applicable only when the processes of activation and recovery have equal opportunity for expression in the electrocardiogram.

The results of this study also suggest that the gradient concept of independence of QRS-T area from activation order is applicable to single leads. When the behavior of leads for both activation and recovery approximated that which would occur with a single central dipole in a circular homogeneous conducting medium, the QRS-T area in individual leads was nearly equal with the two different activation patterns. It appears that the spatial QRS-T area can be independent of activation order only if all leads employed to obtain it provide equal opportunities for expression of activation and recovery. It is unlikely that even corrected vectorcardiographic lead systems accomplish this for all activation and recovery patterns. The failure to find that QRS-T area was perfectly independent of activation order in previous studies may be at least, in part due to different lead behavior in response to activation from that during recovery.

The striking similarity of plots based on QRS area during normal and abnormal activation is of interest aside from its relation to the ventricular gradient. Both plots involved electrodes with the same geometric relation to the heart, and both were subject to the same extracardiac factors including the volume conductor properties of the body. Both QRS areas were the result of events distributed throughout the same ventricular mass. The pattern of distribution of these events differs markedly during normal activation and left bundle branch block, however. Despite the difference, plots of QRS area versus angular lead axis had a similar form in the case studied. This suggests that both activation patterns had a similar degree of eccentricity and a

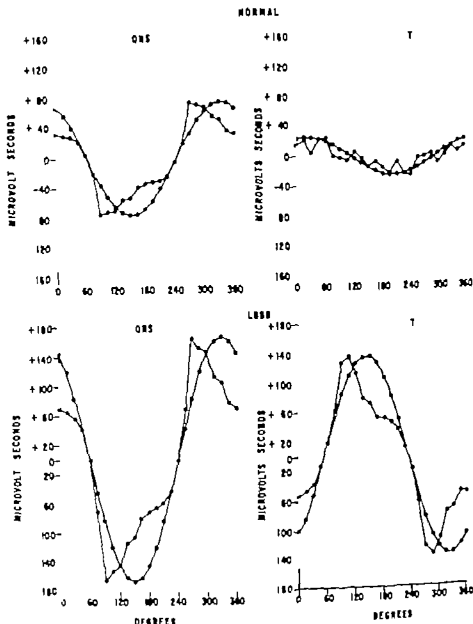


Fig. 4 QRS and T areas plotted as functions of angular lead axis. Values during both normal and abnormal activation correspond most closely to the superimposed sine waves in leads with axes of 45, 60 and 75, 225, 240, and 255 degrees. As explained more fully in the text, this is evidence that the electrocardiographic expressions of excitation and recovery are equally undistorted in these leads. It could be anticipated that total QRS-T areas during normal and abnormal activation would be most nearly alike in these leads and this was true in the case studied

similar mean direction Normal ventricular activation occurring simultaneously in right and left ventricles might be expected to place the average position of events responsible for the QRS complex near the center of the ventricular mass. With left bundle branch block, excitation of right, mid and left portions of the ventricular mass is sequential but the average position of these events might also be expected to be located near the center of the ventricular mass.

It is less evident why the mean direction of normal and abnormal ventricular activation was similar in the case studied. If individual activation of right and left ventricles was normal and only their time phase was altered by bundle branch block, this finding would be expected *It is not certain whether*

this physiologic state existed in the case studied or the similar mean direction of the two activation patterns was a chance occurrence.

Summary

The QRS, ST-T and combined QRS-T area in multiple bipolar chest leads was measured during normal and abnormal activation in a patient with intermittent left bundle branch block. QRS and ST-T areas were plotted as functions of angular lead axis and compared with sine waves which would be the expected form of such plots with a single central dipole in a circular homogeneous conducting medium. Total QRS-T areas during normal and abnormal activation were most nearly alike in leads in which QRS and ST-T areas during both activation states corresponded to sine waves. These results suggest that the gradient concept of QRS-T area independent of activation order is applicable to electrocardiographic leads only when these are equally sensitive to activation and recovery patterns and that it is applicable to single leads.

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Effects of bradykinin on the pulmonary vascular bed of the intact dog

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It is now well established that the nonapeptide bradykinin described in 1949 by Rocha e Silva, Beraldo, and Rosenfeld isolated in pure form in 1960 by Elliott, Lewis, and Horton[2] and synthesized in 1960 by Boissonnas and associates[3] has potent vasoactive properties. Knowledge concerning the pharmacologic and physiologic properties of bradykinin is important because this polypeptide is formed endogenously in man, being released enzymatically from alpha 2 globulin.[4]

The systemic circulatory responses to bradykinin include decrease in total peripheral resistance, decrease in systemic arterial blood pressure, increase in heart rate, increase in stroke volume, and increase in capillary permeability.[5-9] Bradykinin also increases splanchnic,[9] cerebral,[11] and coronary blood flow.[12] It has also been suggested that bradykinin has a direct positive inotropic effect upon the heart.[13]

The effect of bradykinin on the pulmonary vascular bed has received little attention. De Freitas, Faraco, and de Azevedo[6] found that intravenous infusion of bradykinin in ten patients (six of whom had systemic arterial hypertension) resulted in an increase in cardiac output without a significant change in pulmonary artery or left atrial pressures so that calculated pulmonary vascular resistance decreased. They attributed the decrease in pulmonary vascular resistance to active dilatation of the pulmonary vessels but did not designate the site of the dilatation. These investigators did not measure pulmonary blood volume. Bishop, Harris, and Segel[14] found that small doses of bradykinin increased pulmonary vascular resistance at the same time that systemic vascular resistance decreased, whereas larger doses of bradykinin decreased pulmonary as well as systemic vascular resistance. Waaler[15] reported that injection of bradykinin into the pulmonary artery of a perfused isolated canine lung preparation resulted in a small or moderate decrease in pulmonary vascular resistance.

On the basis of the above studies it appears that bradykinin decreases pulmonary vascular resistance. However, in the absence of information on the effect of bradykinin on pulmonary blood volume and on

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pulmonary vein pressure it is unknown whether the decrease in pulmonary vascular resistance is active or passive. The present studies were carried out to learn more about the effects of bradykinin on the pulmonary vascular bed including the pulmonary veins

Materials and methods

Ten adult mongrel dogs weighing an average of 15 7 kilograms (range, 14 1 to 16.8 kilograms) were lightly anesthetized with urethane loosely taped supine to a fluoroscopic table, and given a mixture of 100 per cent oxygen and room air through an endotracheal tube. Cardiac catheters were passed transseptally into a small pulmonary vein and left atrium and into the pulmonary artery and right atrium as described previously [6, 7] Polyethylene tubes were inserted into a femoral artery femoral vein, and into a small vein in the hind paw All of the catheters and the polyethylene tubes were connected to Statham strain gauge transducers (P23Db) and pressures were recorded simultaneously by means of a multichannel oscillographic recorder (Electronics for Medicine) The zero reference was estimated to be from 7 to 9 cm from the top of the fluoroscopic table.

Following control determinations of cardiac output (CO) and pulmonary blood volume (PBV) and while continuously recording mean pressures in the right atrium (P_{ra}) pulmonary artery (P_{pa}) small pulmonary vein (P_{pv}) left atrium (P_{la}) femoral artery (P_{f}) and small systemic vein bradykinin was slowly infused for six minutes into a femoral vein at a constant rate of 10 µg per minute by means of a Harvard constant infusion pump. Cardiac output and pulmonary blood volume were measured at 2 minute intervals during the 6 minutes of infusion and again at 5 minutes and 15 minutes after stopping the infusion

Cardiac output and pulmonary blood volume were measured by the indicator dye dilution technique[18] using indocyanine green (Cardio-green) and the method of analysis described by Hamilton and associates.[1]

Results

The results are summarized in Figs. 1 through 3

Systemic vascular responses The intravenous infusion of bradykinin was associated with a statistically significant increase in heart rate, systemic venous pressure cardiac output, and stroke output and a significant decrease in mean femoral artery pressure and systemic vascular resistance (Figs 1 3) All of the changes occurred within two minutes after starting the infusion of bradykinin, but the stroke output and systemic venous pressure did not increase significantly above control until the four minute test period (Figs. 2

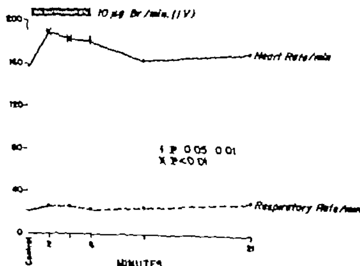


Fig. 1 Effect of intravenous infusion of bradykinin (10 µg per minute) on heart rate and respiratory rate.

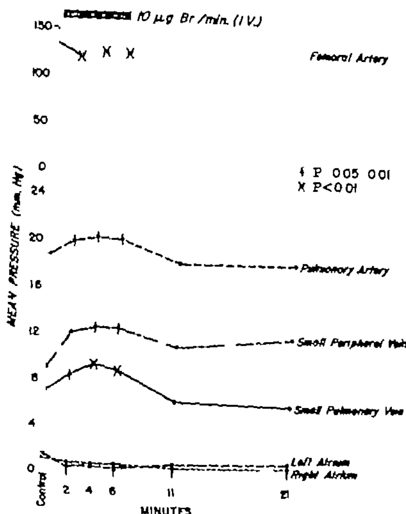


Fig 2. Effect of intravenous infusion of bradykinin (10 µg per minute) on mean pressures recorded simultaneously in the pulmonary vascular bed, right and left atrium, small peripheral vein, and femoral artery

and 3) All values returned to control levels within five minutes after stopping the infusion of bradykinin

Pulmonary vascular responses Two minutes after the beginning of bradykinin infusion pulmonary artery pressure, pulmonary vein pressure, and pulmonary blood volume increased significantly and total pulmonary vascular resistance decreased significantly (Figs. 2 and 3) No significant changes in respiratory rate right atrial pressure left atrial pressure, or pulmonary venous resistance occurred The changes in pulmonary artery pressure pulmonary vein pressure and pulmonary vascular resistance persisted throughout the six minute infusion period. However within five minutes after stopping bradykinin infusion all values had returned to control levels.

Discussion

The systemic vascular responses to the intravenous infusion of bradykinin observed during the present study are in agreement with the findings of previous investigators.[1-4] The decrease in mean systemic arterial blood pressure and in systemic vascular resistance is consistent with the known vasodilating properties of bradykinin The increase in heart rate and systemic venous pressure was probably related to decreased baroreceptor activity secondary to the decrease in arterial blood pressure. The increase in cardiac output and stroke output represented a response to the decrease in systemic vascular resistance but may also have been due in part, to a direct inotropic effect of bradykinin on the heart. The possibility that bradykinin

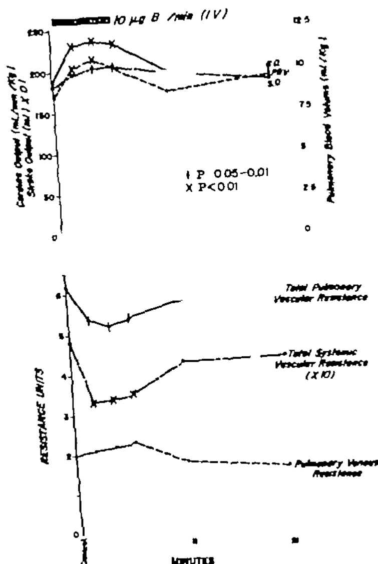


Fig. 3. Effect of intravenous infusion of bradykinin (10 μg per minute) on cardiac output, stroke output, pulmonary blood vol me, and pulmonary and systemic vascular resistances.

exerts an inotropic effect on the heart is supported by the studies of Montague Rosas, and Bohr [19] who found that following autonomic blockade in rats, bradykinin produced an increase in cardiac output in spite of an increase in arterial blood pressure.

Bradykinin administration resulted in a shift of blood into the pulmonary circulation which persisted throughout the six minute infusion period. Since the major portion of the pulmonary blood volume is distributed within the pulmonary veins,[20] it is reasonable to assume that the capacity of the pulmonary venous reservoir increased during bradykinin infusion. The increase in pulmonary venous blood volume could account for the significant increase in pulmonary vein pressure observed in these experiments. The increase in small pulmonary vein pressure while left atrial pressure did not change significantly (left atrial pressure decreased in 6 dogs and did not change in 4 dogs) suggests a throttle valve action of the pulmonary veins. Discordant changes in the dis... acteristics of the left atrium veins cannot explain the i

nary vein pressure without an increase in left atrial pressure as long as the pulmonary vein left atrial vascular segment is in free communication.

Although pulmonary artery pressure increased calculated total pulmonary vascular resistance decreased. Since pulmonary venous resistance did not change the decrease in total pulmonary vascular resistance must have been due to a decrease in pulmonary arteriolar resistance. Thus bradykinin must have dilated the pulmonary arterioles and the increase in pulmonary artery pressure must have been due to hyperkinesis.

The increase in pulmonary venous pressure was probably a passive response to the increase in pulmonary blood volume. However the possibility of an active increase in pulmonary venous tone is not excluded. Nevertheless, it is clear that bradykinin infusion did not result in an active decrease in pulmonary venous tone.

Summary

Intravenous infusion of bradykinin in intact dogs resulted in a significant increase in cardiac output pulmonary blood volume pulmonary artery pressure and pulmonary vein pressure and a significant decrease in systemic and total pulmonary vascular resistances. The decrease in total pulmonary vascular resistance was due to dilatation of the pulmonary arterioles, whereas the increase in pulmonary vein pressure was considered to be due to a shift of blood into the pulmonary venous system. The increase in pulmonary vein pressure with no change in left atrial pressure suggested a throttle valve action of the pulmonary veins, probably at the veno-left atrial junction. No evidence was obtained during these experiments to indicate that bradykinin actively dilates the pulmonary veins.

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Case reports

Fractured intracardiac transvenous pacemaker catheter

An unusual cause of pacemaker failure

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Transvenous pacemakers for treatment of heart block have been used for approximately eight years. As experience with permanent transvenous pacemakers for the long term treatment of complete heart block has increased, so has the number of complications and causes for pacemaker failure. The more common complications and causes of pacemaker failure include electrode malposition, myocardial penetration and perforation, component and battery failure, wire fractures, infection, wound separation and increased threshold.[1-4] We have recently observed an unusual case of pacemaker failure, i.e., disruption of a transvenous pacemaker electrode catheter within the cardiac chambers. Review of the literature revealed only one other similar case. Several unique features of this case and the surgical considerations contained therein prompted this report.

Case report

M. C. G. (Patient No. 280634) was first seen at the Colorado General Hospital (CGH) on Feb. 12, 1967 with a history of second degree heart block being present for the last two months. This disorder was discovered when the patient saw his local physician for treatment of an upper respiratory infection. The patient denied any cardiovascular symptoms and the past history was either negative or noncontributory. The review of systems was negative. The family history revealed two sisters with adult onset diabetes mellitus but no history of heart disease.

Physical examination was totally unremarkable, except for a pulse of 48 beats per minute which was irregular. His blood pressure was 140/68. No cannon waves were observed in the jugular venous pulse and no cardiac murmurs were noted.

The electrocardiogram (ECG) taken on admission revealed second degree block alternating with periods of complete heart block. There was left axis deviation with left superior intraventricular block, and nonspecific ST-T changes. A chest x-ray revealed slightly enlarged left ventricle. The laboratory tests, complete blood count (CBC), urinalysis, electrolytes, blood urea nitrogen (BUN), creatinine, 2 hr pp glucose, serum glutamic oxalacetic transaminase (SGOT), serum lactic dehydrogenase (LDH), and serum cholesterol, were all within normal limits.

Medical management of this patient's heart block was attempted with Isuprel; however, this failed and on Feb. 24, 1967 a transvenous, permanent (the demand type) pacemaker was inserted into the right

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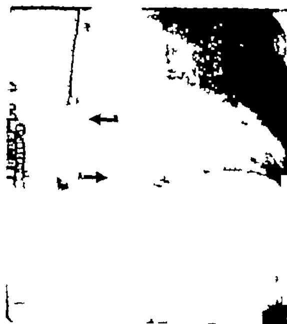


Fig 1 Completely fractured permanent transvenous catheter electrode. 1 Proximal fragment free in right atrium B Distal fragment, fixed i the apex of the right ventricle and fractured tip free in right atrium

ventricle. The patient was discharged asymptomatic on March 1 1967 and it was noted that his heart was following the electrical pacemaker perfectly at a rate of 68 beats per minute.

On follow-up examination on Aug 31, 1967 it was noted that the patient was following his demand transvenous pacemaker with a pulse of 64 beats and an occasional premature ventricular contraction was noted. X-ray examination revealed all wires t be intact and the pacing electrode was in good position at the apex of the right ventricle.

This patient s second admission to the CGH was on Oct 5 1967 when shortly before that date he noticed that his pulse had slowed however he continued to be asymptomatic. Physical examination at that time revealed a pulse of 48. Blood pressure was 140/85. The patient was afebrile and the remainder of the examination was either negative or noncontributory Specifically there ere no clinical finding to suggest tricuspid insufficiency An ECG revealed the amplitude of the pacemaker spike had decreased to one third of that noted on a previous ECG (Aug 31 1967) The pacemaker rate had also slowed from 64 to 40 in the interim two months since the patient' last clinic visit. X-ray examination suggested no battery deterioration and revealed the wires of the electrode catheter to be intact and in good position in the pex of the right ventricle. It was assumed that the pacemaker power pack was the cause of the patient failure t pace, but no specific output studies were done on the pacing unit at this time. The power pack was replaced ith another demand unit on Oct. 13 1967 but the patient continued t pace erratically because of ventricular premature beats. On Oct 18 1967 the pacing catheter was manipulated afterward the patient followed his demand pacemaker but the rhythm was interrupted by an occasional ventricular pre-

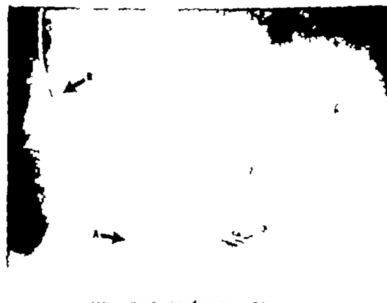


Fig 2 Photographic enlargement of Fig 1

mature beat. The patient returned home and remained asymptomatic, with a pulse of 60 beats per minute. A chest x-ray at the time of discharge from the hospital revealed an intact pacemaker system with the pacing catheter well positioned in the apex of the right ventricle.

In early April, 1968, the patient noticed that his heart rate had dropped to 46 beats per minute and he thus consulted his local physician. A chest x-ray revealed fractured intracardiac pacemaker electrode catheter (Fig. 1). On readmission t CGH on April 12, 1968, x-ray and fluoroscopy revealed the broken pacemaker catheter with the proximal tip free in the right atrium. The broken distal fragment was noted to be fixed in the apex of the right ventricle, hereas its proximal fractured tip was free in the right atrium (Figs. 1 and 2). On April 13 1968, temporary transvenous fixed rate pacemaker as inserted into the right ventricle with minimal difficulty and excellent pacing resulted.

On April 15 1968 an operation was performed to remove the fractured pacemaker wires. At surgery the pericardial space contained 50 c.c. of blood and an area of recent perforation was noted in the body of the right atrium. Palpation of the right atrium revealed three wires to be present within. One was the proximal broken fragment of the original transvenous pacemaker (*A* in Fig. 1), the second was the broken distal fragment (*B* in Fig. 1) free in the right atrium, and the third was the temporary transvenous pacemaker inserted on April 13, 1968. An attempt was made to remove the fractured distal fragment of the transvenous pacemaker catheter by closed procedure, however this could not be accomplished and it was necessary to utilize cardiopulmonary bypass. On opening the right atrium the complete fracture of the pacemaker catheter was confirmed. It was noted that the distal fragment was quite adherent and fibrosed to the tricuspid valve as well as being adherent to the pex of the right ventricle. There ere umerous lot s thin the right trium attached to the fractured fragment of the original transvenous pacemaker. These clot seemed to originate at a point where the tw fractured seg ments overlapped the clots extended one to two inches along the length of the catheter segments. Microscopic examination revealed the clots to be of varying ages, i.e. both fresh and organized thrombus material. The clots were removed and sharp dissection was necessary t remove the distal fractured fragment which was fibrotically adherent to the tricuspid valve. This was done without traumatizing or disrupting the tricuspid val e. The tip of the distal fragment was then removed from the apex of the right ventricle without difficulty. Next, the proximal fractured fragment wa removed via the original chest location (Fig. 3). Two permanent transthoracic coil-spring electrodes were sutured into the left entricular myocardium nd the leads were connected to fixed rate Medtronic unit placed deep beneath the rectus muscle on the left side of the abdomen. Finally the temporary transvenous leads were removed and the patient was noted to pace at rate of 72 beats per min te. Following this procedure, the patient had an uneventf l and satisfactory recovery from his surgery and wa discharged in 12 days pacing faithfully at rate of 72 beats per minute.

Discussion

The reason for pacemaker failure in this case was the disruption of the electrode catheter It was decided to remove the pacemaker fragments in order to avoid potential hazards such as cardiac perfora tion tricuspid valve damage and thrombo-embolic complications. In retrospect, removal of the distal fragment with a snare"

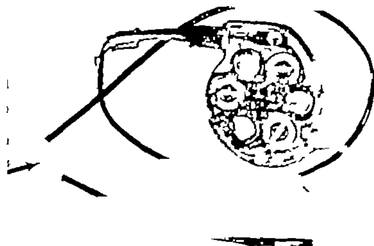


Fig. 3 Pacing unit seen after removal from the patient. The proximal part of the electrode was damaged duri removal.

type catheter could be hazardous because of the potential danger of dislodgement of a mural thrombus and resultant pulmonary emboli or avulsion and damage to the tricuspid valve. Surgical removal utilizing closed techniques was attempted but cardiopulmonary bypass eventually was necessary.

From the case history it is apparent that all of the above complications were possible. The right atrium demonstrated a sealed perforation. Forcible traction upon the fractured distal segment of the electrode catheter would conceivably have damaged the tricuspid valve and dislodged mural thrombi. With cardiopulmonary bypass, the mural thrombi were removed safely and avoidance of the tricuspid valve damage was insured by visualization and sharp dissection. Jensen and associates[3] reported a similar case in 1966. The stylet used for positioning of the electrode catheter in their case had been left in place whereas it had been removed in our case after positioning the electrode catheter. They postulated that the fracture probably resulted from a localized flexion stress secondary to angulation of the catheter in the cavities of the heart. This flexion stress phenomenon is apt to be magnified when there are two points of fixation at the tricuspid valve and at the right ventricular apex. Chardack and co-workers[4] in 1966 reported three stylet fractures causing faulty pacing but since they began removing the stylet from the electrode catheter after positioning it in the right ventricle these fractures have not occurred. These authors reported no cases of disruption of a pacing catheter inside the cardiac cavities. Other authors have not reported catheter electrode fracture if the stylet for positioning the transvenous pacemaker was removed.[5-9] The unique features of our case are the fibrotic fixation of the catheter to the tricuspid valve and the fact that disruption of the electrode catheter had occurred in the absence of the stainless steel positioning stylet.

Summary

Disruption of a permanent transvenous catheter within cardiac chambers is an unusual cause of pacemaker failure. The use of open cardiotomy for removal of the fractured catheter avoids the potential complications seen in the case reported, namely dislodgement of thrombi and tricuspid valve damage secondary to fibrous tissue fixation of the fractured transvenous pacing catheter to the tricuspid valve. Disruption of a permanent transvenous electrode catheter can occur even if the stainless steel stylet, used for positioning has been removed.

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The echocardiogram in a case of mitral stenosis before and after surgery

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The ultrasound cardiogram or echocardiogram of the mitral valve first appeared in the medical literature in 1954. Since then different studies[1-4] have demonstrated the value of this technique in mitral stenosis. During the past year we have used echocardiography as an aid in the diagnosis of rheumatic mitral stenosis in children. The purpose of this paper is to report the echocardiographic findings recorded in a child with mitral stenosis before and after surgery. To the best of our knowledge no such case report has been published for the pediatric age group.

Case report

F. C. is a 13-year-old male patient who has been followed in our Rheumatic Fever Clinic since 1965, because of mitral stenosis. Prior to that time, neither history of rheumatic fever nor the presence of murmur was found.

On Sept. 3, 1967, he was hospitalized at Kings County Medical Center in acute distress. His heart rate was 140 beats per minute, respiratory rate was 45 per minute, and blood pressure was 100/70 mm. Hg. Edema of the lower extremities and venous engorgement of the neck were noted, as well as an enlarged tender liver and signs of pulmonary edema. Precordial bulging with a left parasternal lift was seen. A diastolic thrill was palpable at the apex. The first heart sound was very loud at the apex. The second sound had its maximum intensity at the second left intercostal space and was narrowly split, with an accentuated pulmonic component. An opening snap and a Grade IV/VI harsh diastolic murmur with presystolic accentuation were heard at the apex. A chest roentgenogram showed cardiomegaly and signs of pulmonary edema. The electrocardiogram demonstrated the presence of tachycardia and left atrial enlargement.

The patient was treated for congestive heart failure with bed rest, oxygen, morphine, digoxin, and Mercuhydrin. He responded well to this therapy. The following day a phonocardiogram and echocardiogram were recorded (Fig. 1). The phonocardiogram showed a prolonged Q-S_1 interval (0.085 sec.), a prominent opening snap, and a presystolic murmur. The echocardiogram showed a plateau-like configuration of phase 4. The slope measured 12 mm. per second and the amplitude 22 mm. Cardiac catheterization performed two weeks later revealed pulmonary hypertension, a gradient of 22 mm. Hg between the pulmonary artery wedge and the left ventricular end-diastolic pressure, and a mitral valve area of 1.2 sq. cm. (Table I).

Surgery was performed ten days later. The surgeons confirmed the presence of a constricted mitral orifice and a closed mitral commissurotomy was performed.

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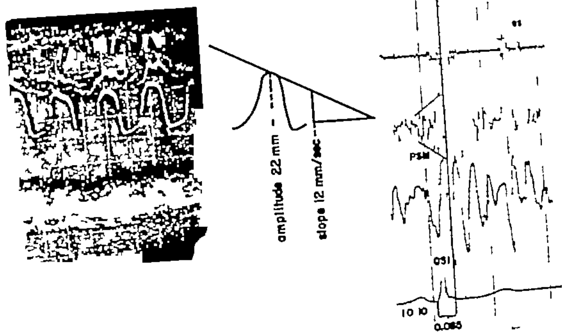

amplitude 22 mm
slope 12 mm/sec
PSM
OS1
10 10
0.085

Fig. 1

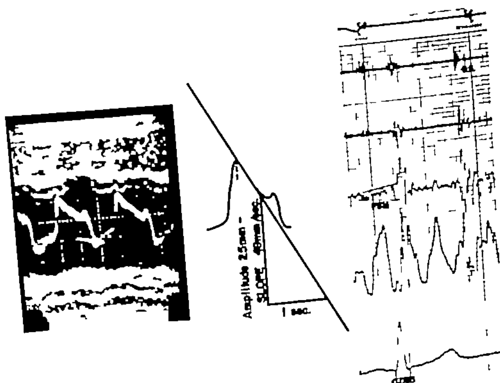

Amplitude 25mm
SLOPE 48mm/sec
1 sec.
PSM
0.085

Table I Hemodynamic data

Parameters	Preoperatively (mm. Hg)	Postoperatively (mm. Hg)
Right Pulmonary Artery	45/23	30/18
Right Pulmonary Wedge	a=39 m=34	a=22 m=18
Main Pulmonary Artery	53/35	30/18
Right Ventricle	55/10	35/8
Right Atrium	=13 m=8	=8 m=6
Left Ventricle, End-Diastolic	12	18
Pulmonary Artery Wedge	34	22
Cardiac Index†	4 0 L./min./M	4 7 L./min./M
MVA‡	1.2	3.6

*Simultaneous recordings.
†Fick principle
‡Mitral valve area expressed in square centimeters and calculated as per Gorlin

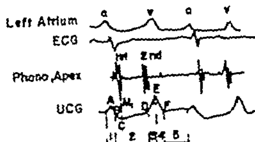


Fig 3 Phonocardiogram (*Phono*) 1st, First heart sound 2nd, second heart sound M mitral component of first heart sound

Ultrasound cardiogram (*UCG*) *A* Atrial wave *B* to *C* represents movement of the anterior mitral leaflet toward closed position during early ventricular systole Point *C* coincides with M *C* to *D* represents the closed position of the anterior mitral leaflet during ventricular systole patroke *D* to *E*, opening movement of the anterior mitral leaflet *E* t *F* the rapid diastolic downstroke during the period of rapid tricular filling Phase 1 is caused by atrial activity and the peak of the *A* wave is the position of maximal opening of the anterior mitral leaflet during trial systole Phase 2 is the systolic wave produced by ventricular contraction. The second heart sound just precedes the point D t be followed by Phase 3 which is the opening movement of the anterior mitral leaflet Point *E* coincides with the opening sound of the mitral valve or opening snap in mitral stenosis It is the maximal opening of the valve Phase 4 represents the movement of the leaflet toward closure during and immediately after the rapid inflow of blood into the ventricle Phase 5 represents the later passive ventricular filling

Six months postoperatively the patient was readmitted to the hospital for re-evaluation. His clinical condition had improved significantly to the extent that he was able to participate in athletic activities. On physical examination the parasternal lift and diastolic thrill were no longer present. The first heart sound decreased in intensity and the second heart sound was of normal intensity and physiologically split. An opening snap and diastolic murmur were still presen but had diminished in intensity

A phonocardiogram recorded on this admission (Fig 2) showed that the Q-S_1 interval (0 065 sec.) had decreased, but an opening snap and a presystolic murmur were still present. The echocardiogram (Fig 2) showed significant change in configuration increase in slope measurement from 12 mm. per second to 49 mm. per second and an increase in amplitude t 25 mm. A second cardiac catheterization was performed (Table I) and demonstrated a decrease in right ventricular pressure, and a gradient of only 4 mm. Hg was now found between the pulmonary artery wedge and left ventricular end-diastolic pressure The calculated mitral valve area had increased to 3.6 sq cm.

Methods

Phonocardiograms were taken with a Schwarzer Cardioscript Model ST 6 S 650/20. Frequency responses of the filter bands were from 250 to 600 c.p.s., 70 to 140 c.p.s., and 30 to 70 c.p.s. Paper speed was 200 mm per second at a gain setting of 6.

Ultrasound cardiograms were recorded on a Physionic VT-400-CA Somascope and photographed with a Tektronix C 27 camera. Five hundred ultrasonic pulses per second at a frequency of 2 megacycles per second (MHz) were transmitted through a bell-shaped transducer 13 mm in diameter made of lead zirconate

The second wave form on a time motion sweep is recorded at a distance of 5 cm from the first one. Different studies[1,3] indicate that the anterior leaflet of the mitral valve is the structure responsible for it.

Fig 3 is a diagrammatic representation of the normal ultrasound cardiogram of the anterior leaflet of the mitral valve in relationship to the electrocardiogram phonocardiogram and left atrial pressure curve.

The two positive deflections, *A* and *E* represent motion towards the transducer (anterior) the two negative deflections *B* and *F* stand for movement away from the transducer (posterior) The positive waves

or upstrokes of the echocardiograms indicate opening of the mitral valve and the negative or downstroke of the curve represents closing movements of the mitral valve. Three important landmarks include (1) point *E* which is the maximal opening and the most anterior position of the anterior mitral valve and coincides with the opening sound (2) the peak of the *A* wave which represents the opening of the anterior mitral valve produced by atrial contractions (3) point *C* which is the most posterior position of the anterior mitral valve and represents the position of the valve in early ventricular systole.

Phase 4 or slope has been found to show the most characteristic changes in mitral stenosis. In normal adults this posterior movement of the anterior leaflet or descent of *E* in millimeters per second occurs at a speed of more than 80 mm. per second.[6] Normal ranges have been reported from 80 to 200 mm per second,[10] 85 to 170 mm per second[3] and 70 to 150 mm per second.[6] The amplitude of the *E* point has been reported to measure between 20 to 30 mm. It has been found by many investigators[4, 8-11] that in mitral stenosis a slow velocity of motion of the anterior leaflet in diastole (reduced slope) is present. This is accompanied by a reduced overall amplitude in cases of calcification or fibrosis.[7]

Discussion

Gustafson[4] correlated the echocardiographic signs of adult patients who had mitral stenosis with their hemodynamic and surgical findings. He found that in patients with sinus rhythm the mean pulmonary arterial and wedge pressures at rest and during exercise had a statistically significant inverse relationship to the descent rate of the anterior leaflet of the mitral valve (phase 4 or slope of the echocardiogram). A direct relationship was found between the calculated mitral valve area and the slope.

It has been shown that the amplitude of *E* (Fig 3) is reduced in cases of calcification of the mitral valve.[12] Edler[7] further showed that in patients with extensive calcification the amplitude did not exceed 15 mm and that in these patients a commissurotomy by the closed technique did not result in a satisfactory change in their slopes following a closed commissurotomy.

He also reported that in patients without calcifications, with sinus rhythm, and an orifice measuring 0.8 to 1.2 sq cm the mean slope was 12.1 mm per second. It increased to 44 mm per second postoperatively. Our patient closely paralleled these findings.

Although no measurements of the echocardiogram of normal children are available, the ones obtained in our laboratory resemble those reported in adults. The abnormal tracing recorded before surgery and its change observed thereafter in our patient mimic those previously reported in adults. The simplicity and safety of this technique make echocardiography a desirable method for the diagnosis and follow up of patients with mitral stenosis.

Summary

The pre- and postoperative phonocardiogram and the hemodynamic and echocardiogram findings of a 13-year-old boy with mitral stenosis were analyzed. It was found in this study, similar to what has been reported in adult patients, that the speed of the diastolic downstroke (slope) of the echocardiogram was a good measure of mitral stenosis. It was also a useful sign in evaluating the result of mitral commissurotomy. The slope was markedly reduced before surgery and was increased significantly after opening of the mitral valve. These patterns were produced by motion of the anterior leaflet of the mitral valve and correlated well with the mitral valve area as found by clinical, phonocardiographic, and hemodynamic findings.

We are indebted to Dr. Jonathan T. Lanman for his criticism and to Mrs. Alma Sapersteln and Miss Loretta Aronson for their assistance.

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Clinical pathologic conference

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Clinical abstract

PROF HEATH A male patient born in 1945 was first admitted to hospital when 11 weeks old with a two week history of increasing pallor and slight jaundice. No further abnormalities were found on physical examination Investigations were carried out and appropriate treatment was given He subsequently attended hospital for treatment at approximately 2 month intervals and remained well for the periods following treatment.

In 1961 at the age of 16 years he was admitted to hospital for investigation of obesity failure to gain height, and dryness of the skin. Examination showed an obese boy whose height (128 cm) was less than that of 97 per cent of normal boys of his age and whose weight (47 kilograms) was less than that of 80 per cent of normal boys of his age. The skin was dry thick pigmented and scaling The hair on his head was dry and coarse the eyebrows pubic, and axillary hair were absent. His voice was deep and husky but there was no undue lethargy or mental retardation. The systemic blood pressure was 100/60 mm Hg The heart appeared normal apart from the presence of a soft systolic murmur The liver was enlarged to 4 fingers breadth below the right costal margin and an enlarged spleen was palpable in the left hypochondrium Various investigations were carried out and further treatment was commenced

In September 1966 he was again admitted to hospital He was now 21 years old and weighed 59 kilograms, his height being 142 cm. Body hair was absent and the genital organs were not developed. There was pigmentation of the skin and buccal mucosa and palpable enlargement of the liver and spleen. The cardiovascular respiratory and central nervous systems appeared normal A surgical operation was performed on his left forearm on Sept. 21 1966. He was discharged home on Oct. 20 1966 but was urgently readmitted 12 days later complaining of shortness of breath expectoration of clear frothy sputum, palpitations and swelling of the abdomen and legs. Examination confirmed the presence of ascites and pitting edema of the legs and showed elevation of the jugular venous pressure. The radial pulse rate was 140 per minute and regular The systolic systemic blood pressure was 140 mm Hg the diastolic pressure was unrecordable. A triple rhythm was audible on auscultation of the heart. The patient failed to respond to treatment and died 17 days after admission

Discussion

DR. WEATHERALL This young man suffered from chronic ill health all his life from an

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illness which was first recognized when he was only 11 weeks old At that time he was admitted to hospital with a two week history of pallor that I equate with anemia. He also had slight jaundice which is probably associated with a raised bilirubin due to hemolysis. These features suggest that he had a hemolytic anemia, probably congenital in type, although an acquired form is possible but much less common at this age. In 1945 not a great deal was known about the different forms of congenital hemolytic anemia. It might have been due to an abnormality of the membranes of the red blood cells such as a congenital spherocytosis. Alternatively it might have been due to some abnormality of the chemistry of the erythrocytes or their contained hemoglobin We must also bear in mind the possibility of a congenital hypoplastic anemia although jaundice is not usually associated with this. Finally anemia with mild icterus may be associated with hypothyroidism Before going on I should like to know the results of hematological investigations that I am sure must have been carried out.

PROF HEATH Representative hemoglobin levels were 3 5 Gm. per cent (24 per cent) in 1945 4.1 Gm. per cent (28 per cent) in 1961 5 7 Gm per cent (39 per cent) in June 1966 and 8 1 Gm. per cent (55 per cent) in November 1966 You will be interested to hear that the reticulocyte count in 1961 was 0 6 per cent. The red cell fragility was normal In 1945 the white cell count was 5 250 per cubic millimeter with a normal differential. The platelet count at that time was 410 000 per cubic millimeter The following year the bone marrow showed a decrease in erythropoietic activity with a shift to the left in the myeloid series.

DR. WEATHERALL Well, these investigations are of course valuable in making the diagnosis. By any standard he had more than a moderate degree of anemia! An important thing to note is that the anemia was persistent in spite of treatment. The reticulocyte count is normal or even slightly subnormal and suggests that this infant did not have a hemolytic anemia. The normal red cell fragility suggests that the shape and size of the erythrocytes were not grossly abnormal. The most interesting finding is that the profound anemia is not associated with any abnormality of the white cells or platelets. The bone marrow showed a selective decrease in the number of red cell precursors. This picture at such an early age is highly suggestive of a congenital red cell hypoplasia of the type described by Diamond and Blackfan in 1938[1] Other causes of selective decrease of red cell precursors such as infections drugs, or diseases of the thymus are most unlikely to operate at this early age.

Accepting this diagnosis of primary red cell anemia we must assume that he was treated with blood transfusions and I see that he was given these every 2 months. He would certainly be treated rather differently for this condition nowadays. Did he have such repeated blood transfusions during the entire period from 1945 to 1961?

PROF HEATH Yes.

DR. WEATHERALL Well, if we assume that there is some 250 mg of iron in each unit of blood we can only conclude that during that time he received a colossal amount of iron Did he have any other form of treatment?

PROF HEATH He had short courses of ferrous sulfate and proteolyzed liver folic acid in 1947 vitamin B_{12} in 1950 adrenocorticotropic hormone in 1953 stilbestrol in 1956 and methyltestosterone in 1959

DR. WEATHERALL I should like to know if estimations of serum iron were carried out.

PROF HEATH In 1961 the serum iron was 325 µg per cent and five years later it was 327 µg per cent with a serum iron-combining capacity of 318 µg per cent.

DR. WEATHERALL These levels are greatly elevated above the upper limit of normal of about 150 µg per cent. Interestingly enough this iron-combining capacity is slightly reduced suggesting that there may have been some liver damage. All of this raises in my mind the possibility of his having developed a hemochromatosis secondary to the repeated blood transfusions.

If we now return to the clinical picture in 1961 of obesity dryness of the skin absence of the eyebrows and the other signs included in the clinical summary we have to conclude that he had developed

hypothyroidism The absence of pubic and axillary hair also suggest a gonadal deficiency All anemic children kept alive by repeated blood transfusions tend to have a delayed puberty with underactivity of the pituitary gland He appears to have developed multiple endocrine deficiencies. Were investigations carried out to confirm this?

PROF HEATH In February 1961 his serum cholesterol level was 215 mg per cent, but after treatment with 0 3 mg of thyroxine daily it fell to 141 mg per cent in the following month Over a similar period his serum protein bound iodine rose from 0 7 to 10 5 μg per cent.

Urinary 17-oxysteroids were at a level of 2 mg per 24 hours and urinary 17 oxygenic steroids were 7 mg per 24 hours

You may also be interested to hear that glucose tolerence tests were carried out in 1954 and 1964 In the earlier test the fasting blood sugar was 80 mg per cent rising to 200 mg per cent in 45 minutes and falling to normal levels in 2½ hours In the later test the fasting blood sugar was 118 mg per cent rising to 235 mg per cent in 1 hour and it still remained at an elevated level of 191 mg per cent after 2½ hours

DR. WEATHERALL All these tests indicate multiple endocrine deficiencies involving the thyroid and pituitary glands and the pancreas. Clearly he was now in a prediabetic state. I suggest that he had developed hemochromatosis secondary to the repeated blood transfusions he had received for his congenital primary red cell anemia I note that he had an enlarged liver and spleen almost certainly due to deposition of excess iron. I would suspect that some effort must have been made to treat this hemochromatosis.

PROF HEATH In 1964 he was indeed given chelating agents in an attempt to mobilize the iron He had courses of desferrioxamine mesylate and diethylenetriaminopentacetic acid was given with the blood transfusions. The urine gave a strongly positive test for iron.

DR. WEATHERALL What was the surgical operation carried out on the left forearm?

PROF HEATH A Quinton Scribner arteriovenous shunt was created to facilitate blood transfusion and the withdrawal of blood for investigation.

DR. WEATHERALL Perhaps we could now consider his terminal illness. On admission on October 20 1966 he had shortness of breath and was coughing up frothy sputum He had palpitations and swelling of the abdomen and legs. Clearly he was in severe cardiac failure. I note that the heart was normal on clinical examination apart from a triple rhythm and a soft apical systolic murmur I think his acute cardiac failure is due to cardiac hemochromatosis, iron being laid down in his myocardium in the same way as it was laid down in the endocrine organs. May I see his electrocardiogram (ECG)? (This was shown [Fig 1]) This shows surprisingly little. He was in sinus tachycardia when this was taken and there are inverted T waves in Leads V to V_4 and in Lead aV_L What did the chest radiograph show? (This was shown [Fig 2]) This shows slight generalized cardiac enlargement with pulmonary edema and small bilateral posterior costophrenic effusions. In conclusion I think he

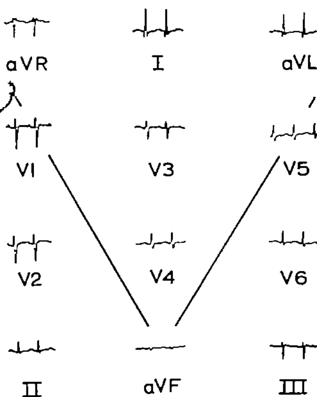


Fig 1 Electrocardiogram recorded on Sept. 26, 1966.

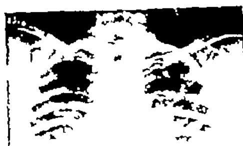


Fig 2 Chest radiograph taken on Nov 3 1966.

had generalized hemochromatosis with involvement of the myocardium

DR WOODROW Was there any familial history of anemia or any disorder of iron metabolism?

DR KAY He was the second child of healthy unrelated parents. There was no family history of metabolic disease or anemia.

DR BAKER BATES Do you think the arteriovenous anastomosis contributed to his death?

DR. WEATHERALL The diastolic blood pressure was unrecordable so that he must have had a collapsing pulse, and this suggests that there must have been hemodynamic changes following the creation of the anastomosis. When one remembers that his myocardium contained a great deal of iron it is likely that the shunt proved a further embarrassment to the action of the heart.

DR. WYN JONES The ECG looks strikingly normal to me. Do you think this is in keeping with a myocardium loaded with iron? I had the impression that the electrocardiogram in hemochromatosis is fairly characteristic.

DR. WEATHERALL I think the ECG in these cases is very variable. Sometimes it can look surprisingly normal even though the heart muscle is subsequently shown to contain a great deal of iron

PROF HEATH Could we now ask Dr Kay the *vox dei* in this case as to what was found at necropsy

DR. KAY At necropsy the body was pigmented and there was absence of the axillary and pubic hair There was obesity of the trunk The genitalia were small The arteriovenous shunt created in the left forearm was not thrombosed. There was evidence of cardiac failure in that there was pitting edema of the legs, ascites, and bilateral pleural effusions.

Many of the organs were of a striking rusty discoloration Thus the liver was brown and contained much hemosiderin for when portions of it were immersed in a solution of potassium ferrocyanide and hydrochloric acid they turned blue. This is Perls test or the Prussian blue reaction for ferric iron. On chemical analysis the liver was found to contain 3.3 per cent of its dry weight of ferric iron which is 50 times the normal iron content of this organ The liver was enlarged weighing 2,200 grams and its cut surface showed a fine regular nodularity Histological sections revealed a micronodular or portal cirrhosis with circumscribed islands of parenchymal cells separated by broad bands of fibrous tissue containing proliferated bile ducts and amorphous masses of hemosiderin Iron was found in the hepatic parenchymal cells, the Kupffer cells, and in macrophages in the perinodular connective tissue There was even a scattering of iron pigment in the epithelial cells lining the proliferated bile ducts. These are the features of hemochromatosis of the liver The gall bladder contained a large number of pigment stones.

The heart was of normal weight (300 grams) Neither ventricle was hypertrophied the free wall of the right ventricle weighed 50 grams. The apparent enlargement of the heart noted on radiographic examination was due to dilatation of both ventricles, this being an indication of cardiac failure. The myocardium was rusty brown in color and chemical analysis showed it to contain 1.8 per cent of its dry weight of ferric iron which is about 45 times the upper limit of normal given by



Fig 3 Heart. Myocardial fibers widely separated by cellular fibrous tissue containing accumulations of hemosiderin. (Hematoxylin and eosin, ×135.)



Fig 4 Heart showing perinuclear distribution of iron pigment within muscle fibers. Hemosiderin-laden macrophages in interstitial tissue. (Prussian blue method. ×550.)

Sheldon in 1935 Histological sections of the anterior wall of the left ventricle revealed widespread replacement of muscle fibers by cellular fibrous tissue containing hemosiderin laden macrophages (Fig 3) There was also a large amount of hemosiderin within the myocardial fibers This iron pigment assumed a characteristic distribution either side of the nuclei of the muscle fibers (Fig 4) this is characteristic of cardiac hemochromatosis.

The lungs were firm due to edema Histological sections showed edema coagulum in the alveolar spaces and accumulations of hemosiderin laden cells in the interstitial spaces and alveolar septa (Fig 5)

The cut surface of the enlarged spleen (465 grams) was brown and gave a positive Perls reaction. Histologically most of the iron pigment was confined to the red pulp The lymphoid tissue was largely free from iron deposition. There was also iron impregnation of the fibrous trabeculae and blood vessels.

The pancreas was also loaded with iron pigment. Histological examination showed widespread replacement of the pancreatic parenchyma by fibro-fatty tissue loaded with hemosiderin (Fig 6) The islets of Langerhans appeared to have atrophied but to a lesser degree than the exocrine parenchyma Most of the iron was found in the connective tissues but small quantities were seen in the epithelial cells of the exocrine acini and ducts and in the islet cells.

The bone marrow of the shaft of the femur and the vertebral bodies was brown in color Histologic examination showed a cellular marrow containing normal numbers of megakaryocytes and leukocyte precursors but there was a striking paucity of erythrocyte precursors. There were accumulations of hemosiderin in macrophages throughout the marrow

The thyroid gland was grossly atrophied weighing 2 6 grams instead of the normal 30 grams. It consisted of fibrous tissue



Fig. 5. Lung. Edema coagulum in alveolar spaces and interstitial collections of hemosiderin laden macrophages. (Hematoxylin and eosin. ×135.)



Fig. 6. Pancreas. Widespread replacement of exocrine parenchymal elements by fibro-fatty tissue laden with siderophages. Well-preserved islet of Langerhans in center of picture. (Hematoxylin and eosin. ×135.)

impregnated with masses of iron pigment (Fig. 7). No thyroid epithelial tissue was found.

The pituitary gland was atrophied weighing 260 milligrams instead of the normal 500 milligrams. The cells of the adenohypophysis were laden with ferric iron. The neurohypophysis was free from iron deposition. The adrenals were normal in size weighing 12 grams together. They were brown in color and gave a positive Perls reaction. Iron was present in the cells of the zona glomerulosa, zona fasciculata, and zona reticularis.

The kidneys appeared normal on gross examination but gave a faintly positive reaction for ferric iron which was found in the cells lining the distal convoluted tubules.

This patient with hypoplastic anemia or erythrogenesis imperfecta as it is sometimes called, was reputed to have received 480 bottles of blood throughout his life. This is equivalent to his having received 120 Gm. of iron intravenously. Such iron passes initially into cells of the reticuloendothelial system and then into the parenchyma of affected organs, where it brings about tissue damage. Hence here we have an example of secondary hemochromatosis leading to death from cardiac failure due to involvement of the heart.

PROF. HEATH: Don't you think that the term hemochromatosis ought to be restricted to the primary disease of iron metabolism? Wouldn't it be better to call the present condition transfusional hemosiderosis?

DR. KAY: I think we ought to keep the term secondary hemochromatosis because this implies the deposition of iron in tissues with resultant damage. Hemosiderosis suggests iron deposition without associated damage. I think the disease to which you are referring should be called idiopathic hemochromatosis.

DR. HASLETON: You have demonstrated gross changes in the myocardium ye



Fig. 7. Thyroid. Consists of cords of fibrous tissue heavily laden with hemosiderin. Total atrophy of epithelial acini. (Hematoxylin and eosin. ×135.)

ECG was normal. Can you explain this discrepancy?

DR. KAY: In fact, the ECG showed inverted T waves which I would think was abnormal. I hope that my ECG does not have inverted T waves! I assume that he had iron deposits in the conduction system but I have not verified this histologically.

DR. CRUICKSHANK: From time to time I have carried out necropsies on patients who had the idiopathic form of hemochromatosis and in these cases accumulation of hemosiderin in the myocardium was not impressive. Instead these patients died with liver failure, hemorrhage from varices, or from diabetic coma. One patient had a primary carcinoma of the liver. Do you think that the excessive accumulation of hemosiderin in the myocardium such as you describe is peculiar to the secondary form of hemochromatosis?

DR. KAY: I think you must have had an atypical series of cases because in about 30 per cent of cases of idiopathic hemochromatosis the cause of death is cardiac failure and such cases show considerable hemochromatosis of the myocardium. About 15 per cent of such patients with idiopathic hemochromatosis present with signs and symptoms attributable to cardiac involvement.[5] I don't regard the case we have seen today as in any way atypical in regard to the heart.

DR. WYN JONES: In mitral stenosis with cardiac failure there is hemosiderosis of the lungs and the pulmonary changes you have demonstrated here could be accounted for on the basis of congestion in the lung.

DR. KAY: Not really because the pulmonary vasculature was normal and there was no evidence of chronic left ventricular failure.

PROF. HEATH: In pure red cell anemia there is commonly associated some abnormality of the thymus such as a thymoma. What was the state of the thymus in the present case?

DR. KAY: A thymoma is found in about one third of the cases of acquired pure red cell anemia. There is no association between the thymus and this congenital form of red cell anemia. In this case the thymus was normal macroscopically.

DR. WEATHERALL: We ought to mention that if this patient were to present now he would be treated with steroids rather than repeated blood transfusions. These cases seem to show a reasonable response to therapy provided treatment with steroids is started within the first two years of life.

DIAGNOSIS: *Cardiac failure due to secondary hemochromatosis following repeated blood transfusions for congenital red cell hypoplastic anemia.*

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Fundamentals of clinical cardiology

Gallop rhythm

Hemodynamic and clinical correlation

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Gallop rhythm is defined as the presence of three sounds in succession separated by appropriate intervals to give rise to a cadence of a galloping horse. Assuming this auditory reference to be accurate, the necessary three sounds may be formed by the two normal heart sounds plus an additional sound in early or late diastole. In the past a midsystolic sound which is often extracardiac in origin has been considered as a systolic gallop rhythm. This form of gallop rhythm has no consistent clinical or hemodynamic significance and does not merit further discussion.

Gallop rhythm may be divided into two types: (1) ventricular gallop and (2) atrial gallop. Ventricular gallop occurs in early diastole at about the peak of rapid filling of the ventricle. It has been previously called protodiastolic gallop. It is indeed a pathologic counterpart of the third heart sound (S_3) which is often noted in normal children and young adults. The differentiation is based largely on associated factors such as age, heart rate, and obvious evidence of heart disease. The physiologic third sound is rare over the age of 30 years and virtually unknown after 40 years. Other evidences of cardiac disease are generally self-evident and help in differentiation between physiologic and pathologic S_3. However, in children with suspected myocardial disease, the differentiation may be difficult and of more than academic interest. Atrial or presystolic gallop is closely related to atrial systole and represents the fourth sound (S_4), which is normally inaudible.

In addition to the isolated ventricular (S_3) and atrial (S_4) types of gallop rhythms there are instances when the two sounds may overlap and give rise to a summation gallop (SG). This is brought about by a short diastolic period as a result of excessive tachycardia with or without associated first degree atrioventricular block. It represents a coincidence of the two phases of ventricular filling resulting from an abbreviated diastole and/or prolonged P-R interval. When both additional sounds are separately perceived, a quadruple rhythm ensues.

Review of the literature

The first clear description of gallop rhythm was written by Potain in 1880, who credited his teacher Bouillaud for

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*The work was done under the tenure of a National Institutes of Health Special Fellowship in Cardiology.

coining the term. Potain postulated the mechanisms of diastolic gallop with remarkable insight in cardiac physiology and wrote: normally after the ventricle has emptied, it then dilates, filling with blood brought partly by the vis-a tergo and partly by atrial contraction which completes ventricular filling. The atrium therefore normally plays an accessory role. But when the ventricle is little distended, the action of the atrium becomes of greater importance, for if little blood arrives in the ventricle, the role of the atrium is more active and the sudden lift during its contraction, which is presumably our gallop sound. It is not exclusively a pathological phenomenon, but it is rather an exaggeration of a normal phenomenon. If cardiac muscle loses its tonicity, the ventricle in dilating arrives rapidly to the point where resistance of the fibers of its wall limits its distention, then suddenly it becomes arrested and produces a tension shock and gallop sound.

Despite this brilliant assessment, the subsequent literature is filled with gross inaccuracies resulting partly from confusion with triple rhythm due to various other causes such as splitting of first or second sounds, early systolic clicks, and the opening snap of mitral valve. Broadbent, who enjoyed a reputation as a great clinician, made no statement of gallop rhythm in his book entitled *Heart Disease with Special Reference to Prognosis and Treatment* published in 1900. In 1925, Mackenzie[3] in the revised edition of his book, *Diseases of the Heart*, mentioned just in passing the prognostic significance of gallop sounds. In the third edition of their text, *Diseases of the Chest and the Principles of Physical Diagnosis* (1927), Norris and Landis[4] considered among causes of gallop rhythm early stages of mitral obstruction and observed that electrocardiographically it was almost universally characterized by a split R wave. They considered the gallop rhythm the distress signal of the heart. In 1937 Lewis[5] noted that gallop rhythm represented heart failure with no constant underlying lesion though hypertrophy of the atrium was frequent. The same year Fishberg[6] discussed the subject with clarity in his book, *Heart Failure*.

With the advent of improved graphic techniques of recording heart sounds, numerous publications have appeared in the past two decades. The poor prognostic significance of the gallop sound was emphasized.[7,8] Many authors noted frequent occurrence of presystolic or atrial gallop in systemic hypertension without evidence of heart failure and its persistence for a number of years.[9,10] The prevalence of abnormal third sound in mitral incompetence without heart failure was also reported.[11] The effects of changes in venous return on the atrial gallop have been investigated. It was shown that a decrease in venous return moved the atrial gallop sound closer to the succeeding first sound and that an augmentation in venous return prolonged the interval between these two sounds.[12] There have been relatively few reports correlating the gallop sounds with hemodynamics. It has been pointed out that atrial pressures are invariably elevated when gallop sounds are audible.[14] Correlation between atrial sound and raised left ventricular end-diastolic pressure has been reported in patients with aortic stenosis.[15]

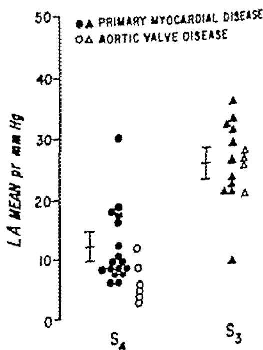


Fig. 1. Left atrial mean pressure in patients with atrial (S_4) gallop and in those with ventricular (S_3) gallop.

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Table I. Observations on patients with gallop sounds

Parameter	Primary myocardial disease (28 patients)		Aortic valve disease (10 patients)		Normal
	S_3	S_4	S_3	S_4	
Left atrial pressures					
mean	12.02 ± 2.28	25.3 ± 2.1	7.2 ± 1.8	25.0 ± 2.2	7.9 (2–12)
"a" wave	19.2 ± 4.6	27.2 ± 3.7	15.3 ± 3.8	29.4 ± 3.6	10.4 (4–16)
"a" wave minus mean	7.18 ± 1.07	3.1 ± 2.2	8.1 ± 2.0	4.4 ± 1.6	3.4 (1–7)
"v" wave	16.7 ± 2.18	38.5 ± 4.1	11.8 ± 2.2	33.2 ± 1.8	12.8 (6–12)
"v"–"y" press	5.4 ± 1.0	23.1 ± 2.8	4.2 ± 2.2	22.4 ± 3.1	
peak v/y slope	60.0 ± 18.5	370 ± 43.4	71.6 ± 11.6	525 ± 52.0	80–170†
Cardiac index	2.58 ± 0.07	1.74 ± 0.14	3.0 ± 0.16	2.1 ± 0.2	>2.5†
LV cavity ratio wall thickness	3.3 ± 0.6	7.56 ± 0.76	3.5 ± 0.4	7.2 ± 0.52	>6.5‡

*Data of Braunwald and associates.[13]
†Data from our laboratory.
‡Data of Levine and associates.

Present study

The hemodynamic determinants of gallop sounds in patients with primary myocardial disease have been previously reported from our laboratory. The present study has been extended to include a group of patients with aortic valve disease. Those patients with any evidence of mitral valve involvement are excluded since the gallop sounds are intimately related to ventricular filling. Furthermore, the magnitude of left atrial mean pressure in patients without mitral valve disease may faithfully reflect that of left ventricular filling pressures.

Detailed clinical, hemodynamic, and angiographic observations have been correlated with the gallop sounds in 28 patients with myocardial disease and in 10 with aortic valve disease. The results are summarized in Table I.

The cardiac index in patients with atrial gallop was maintained close to the normal values, although it was reduced in patients with ventricular gallop. The former group had normal left atrial pressure, while the latter group had a significantly elevated pressure (Fig. 1). The combination of high left atrial pressure and low cardiac index in these patients may be accepted as hemodynamic evidence for ventricular decompensation. Thus, the patients with ventricular gallop had clear evidence of heart failure.

In order to explain the basis for these findings in the two groups, we examined the characteristics of diastolic filling of the left ventricle. This was generally easier to judge from the left atrial pressure pulse since the rate of atrial emptying would be expected to mirror the rate of ventricular filling. The peak slope of v to y in 12 normal subjects in our laboratory has been found to vary between 80 to 170 *mm. Hg* per second. The pressure drop from the peak "v" wave to the "y" nadir in the left atrial pressure pulse was consistently greater in patients with ventricular gallop than in those with normal hemodynamics. The exaggerated slope in patients with ventricular gallop indicates a rapid rate of early ventricular filling. In contrast, the patients with atrial gallop had a small pressure drop at a slower rate, indicating a reduced rate of early ventricular filling (Fig. 2).

Changes in the left ventricular cavitary size relative to the wall thickness were assessed angiographically by the method of Levine and associates.[14] These authors reported that values in normal su

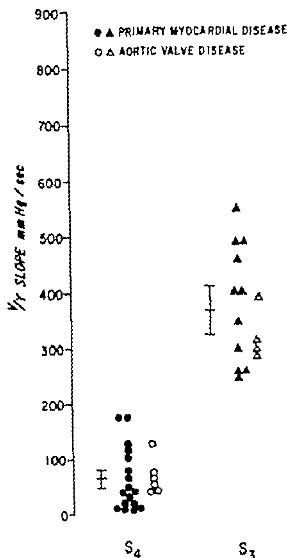


Fig. 2. Peak slope of v/y from left atrial pressure pulse in the two groups of patients.

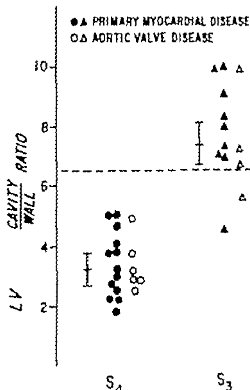


Fig. 3. Ratio of LV cavity-to-wall thickness by the method of Levine and associates[11] in the two groups of patients.

should be above 6.5. A higher cavity-to-wall ratio (greater than 6.5) indicates greater left ventricular cavitary dilatation whereas a lower ratio signifies a greater degree of ventricular hypertrophy. In our series a high ratio was noted in patients with ventricular gallop while a low ratio was observed in those with atrial gallop (Fig. 3).

Clinical significance

Based on this study, it is suggested that the presence of atrial gallop signifies a decrease of compliance, generally from ventricular hypertrophy but this may also result from myocardial ischemia or fibrosis. The atrial gallop alone does not indicate heart failure which is usually characterized by an elevated ventricular filling pressure associated with a reduced cardiac output. Hemodynamically, the patients with atrial gallop usually have normal left atrial mean pressure and a normal cardiac output. They may have no symptoms of cardiac decompensation for several years despite the presence of atrial gallop rhythm. It must be recognized that these patients depend on a powerful atrial boost to maintain adequate cardiac output and that the development of cardiac arrhythmias (e.g., atrial fibrillation) may have deleterious consequences.

On the other hand, in patients with ventricular gallop there is almost always a rise in left atrial mean and left ventricular end-diastolic pressures associated with a fall in cardiac output. These patients generally have other clinical manifestations of cardiac decompensation and may often be seriously ill requiring a vigorous therapeutic management. The hemodynamic

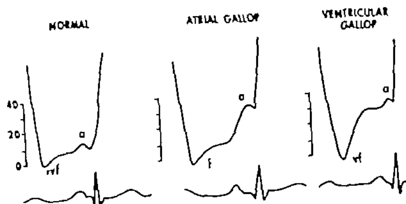


Fig. 4 Diagrammatic representation of the left ventricular diastolic pressure pulse in normal subjects in patients with atrial gallop, and in those with ventricular gallop (*rvf* rapid ventricular filling atrial systolic wave).

significance of quadruple rhythm and summation gallop appears to be similar to or even more serious than that of ventricular gallop alone.

Fig 4 depicts diagrammatic representation of the left ventricular diastolic pressure pulse in normal subjects and in patients with either atrial or ventricular gallop The left ventricular end-diastolic pressure may be raised by several ways and the hemodynamic connotations are indeed different in each situation Thus, ventricular diastolic pressure corresponding to a wave in the left atrial pressure may be the result of prominent atrial boost to a less compliant ventricle. On the other hand the diastolic pressure in the ventricle prior to the atrial systole may itself be significantly elevated with little influence from the "a wave. The hemodynamic significance of these two examples where the end-diastolic pressure may be equally elevated is indeed quite different The former represents merely loss of compliance, while the latter cardiac decompensation with probable increase in end systolic volume. Similarly a rapid ventricular filling with a prominent atrial boost provides the basis for quadruple rhythm. The summation gallop is associated with abbreviated diastolic filling period from rapid heart rates or from prolonged P R intervals in the face of cardiac decompensation when the early rapid filling and atrial systole are superimposed (Fig 5)

In our experience a correlative analysis of heart sounds with hemodynamic findings is useful in estimating the hemodynamic state of patients with myocardial disease or aortic valve disease. There is paucity of follow-up studies on patients with gallop sounds. It is hoped that such future studies will include correlated phonocardiographic and hemodynamic data.

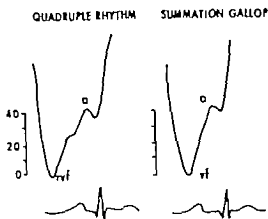


Fig. 5 Diagram of ventricular pressure pulse in diastole, in presence of quadruple rhythm and of summation gallop (*rvf* rapid ventricular filling atrial systolic wave).

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff, Alan F. Lyon, and Julian Frieden

The treatment of tachyarrhythmias by artificial cardiac pacing

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In 1960 Zoll, Linenthal, and Zarsky[1] and Schwedel, Escher, and Furman using closed-chest and transvenous right ventricular endocardial stimulation respectively reported that fixed rate asynchronous pacing at normal heart rates prevented ventricular tachycardia and fibrillation in patients with heart block and bradycardia. By 1964 it was appreciated that ventricular pacing at normal or rapid rates, could diminish or abolish ventricular extrasystoles, tachycardias, or fibrillation in the presence or absence of heart block; also that the combined use of pacing and antiarrhythmic drugs could improve the effectiveness of either modality in treating supraventricular as well as ventricular tachyarrhythmias. Current management has been implemented by the introduction of demand, paired, and coupled pacing by new techniques of electrode insertion and also by right atrial stimulation when atrioventricular conduction is intact.

There are two modes by which pacing may control tachyarrhythmias. In the first, stimulation is used to block or override spontaneous irregular or rapid rhythms. Applied at relatively rapid rates it will (1) reduce myocardial ischemia, particularly with a prior bradycardia, by increasing cardiac output and coronary artery perfusion; (2) diminish the nonrefractory time during which an ectopic focus can arise; (3) inactivate a focus or interrupt conduction by premature depolarization; (4) depress spontaneous pacemaker activity; and (5) impose a single regularly repetitive pattern for depolarization and recovery. In the second approach, pacing is used as a standby. Applied at low or normal rates, preferably in the demand mode, it protects against bradycardia or asystole in the course of a mixed arrhythmia or following treatment of a tachyarrhythmia by drugs.

Most tachyarrhythmias are transient and require only temporary pacing. The method of choice, for a closed-chest approach, is a transvenous right ventricular or right atrial endocardial electrode. The available routes of entry include the external and internal jugular and brachial veins by cut-down techniques with insertion of radiopaque electrodes under fluoroscopy; the external jugular, subclavian, brachial, and femoral veins by percutaneous needle methods with radiopaque electrodes inserted under fluoroscopy; the subclavian (supraclavicular and infraclavicular routes), external jugular and brachial veins by percutaneous needle methods with semifloating electrodes inserted at the bedside under electrocardiographic control. Properly utilized, a subclavian vein with a semifloating electrode is probably the easiest and most rapid approach. The femoral route, with a

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radiopaque electrode is equally effective for short term use when there is access to fluoroscopy The external jugular is reserved for prolonged temporary or permanent use External closed-chest pacing or transthoracic percutaneous myocardial wires are used only where no other methods are available or speed is imperative Cardiac surgical patients should have removable myocardial wires placed during thoracotomy

All of these exteriorized electrode systems must be protected against contact with current sources other than their own pulse generators. All electrical equipment must be compatible and well grounded particularly the electrocardiograph recorder used for intracardiac monitoring

The pulse generators used for temporary pacing whether in AC powered monitor systems or battery powered transistorized packs (Medtronic Electrodyne General Electric) almost all operate in the fixed rate asynchronous mode Although they can be set at a wide range of rates competitive pacing may occur if used during an irregular tachyarrhythmia. External stimulus-blocking demand pulse generators will not permit this (AC powered Electrodyne or American Optical battery powered Medtronic or Cordis) When the patient s heart rate is slow they function in the asynchronous mode However spontaneous rhythms at rapid rates block the output stimulus of the pacemaker and abolish competitive stimuli The output block is maintained as long as the spontaneous R R interval is above the rate of the pacemaker When the spontaneous rate falls below the pacemaker rate fixed rate pacing is resumed Therefore this mode is not only a safer form of pacing in any rapid or irregular rhythm but it is ideal for use as a standby safeguard at normal or elevated rates. Unfortunately it is applicable at present only to ventricular pacing as most models require an intracardiac voltage of about 2 mv to trigger output blocking by the sensor circuit. This is an amplitude not consistently found in the atrium

A good pacing threshhold for a well positioned temporary electrode is 0.3 to 1 0 Ma. Above 1.5 Ma the electrode should be repositioned If possible

In order to effect complete overriding and capture of a rhythm the pacemaker rate must be at least 10 to 20 beats above the spontaneous rate. When the underlying rhythm is a sinus or nodal bradycardia or an A V block with a slow idioventricular rate fixed rate pacing at 60 to 80 beats per minute usually will protect against ventricular extrasystoles, tachycardias or fibrillation When a transmitted atrial or a ventricular rate is more rapid or very irregular stimulation at 90 to 140 beats per minute may be required. Atrial pacing is excellent for ventricular tachyarrhythmias when A V conduction is intact or in transmitted atrial arrhythmias. Ventricular pacing must be used when stable transvenous pacing from the atrium is not possible when there is A V block, or when demand pacing is desired In rapid asynchronous ventricular pacing of transmitted supraventricular tachycardias, retrograde atrial depolarization may act to block the aberrant atrial conduction and permit capture of the ventricular rate or conversion to normal sinus rhythm. Conversion to sinus rhythm has been reported in the Wolff Parkinson White syndrome when competitive or coupled pacing interjected a ventricular impulse 260 to 290 msec after the onset of a previous spontaneous QRS

The etiology of the tachyarrhythmia does not appear to be a major factor in most successful cases of control by overriding pacing Good responses have been reported in tachycardias consequent to myocardial anoxia from a rate-dependent low cardiac output to myocardial injury from infarction trauma infection or surgery to electrolyte imbalance as seen in uremia, hyperkalemia or hypomagnesemia or to drug toxicity from digitalis, quinidine and thioridazine Tachyarrhythmias produced by sympathomimetic amines (epinephrine ephedrine isoproterenol) used in the treatment of bradycardias or hypotension may be enhanced rather than controlled by pacing particularly if competition is allowed and stimuli fall in the vulnerable or supranormal phase of the electrical cycle In all cases particularly this last pacing at normal or overriding rates is safer when applied in the demand mode

The demand mode is also preferred when

pacing is employed as a standby during pharmacologic treatment of an arrhythmia. In patients with intact A-V conduction but sensitive to digitalis or quinidine ventricular pacing protects against an induced atrioventricular delay or block. In propranolol or other beta adrenergic blockade-induced sinus bradycardias, or in the treatment of supraventricular tachycardias by the potentially dangerous combination of digitalis and propranolol pacing will maintain the ventricular rate even should atrial asystole occur. In pre-existent atrioventricular block, pacing will prevent ventricular bradycardia or asystole from reduction of ventricular automaticity by lidocaine or procainamide.

Pacing at a high overriding rate is not well tolerated by a diseased heart and as with a spontaneous tachyarrhythmia may result in angina, hypotension or congestive failure. Though it may provide a better cardiac output than a grossly irregular rapid rate and protect against further degeneration of the rhythm it should not be sustained for longer than necessary. Some patients encounter difficulty even at 90 beats per minute since rapid rates reduce ventricular filling time and increase cardiac oxygen consumption and cardiac work. Atrial pacing has a physiologic advantage over ventricular pacing in that it preserves atrioventricular synchrony and may result in patients in congestive failure in an improved cardiac output. Once paced control has been established it often can be sustained despite a gradual reduction in the overriding rate to a level below that of the spontaneous tachyarrhythmia. At times initially required rates of 120 to 140 can be gradually reduced to 90 to 110 beats per minute before escape occurs. Where a sustained reduction cannot be realized rapidly or where dependence on pacing alone is undesirable or ineffective, a combination of antiarrhythmic drugs and overriding pacing may be effective. In tachycardias that are too rapid to be overridden or captured and are unresponsive to drugs, cardioversion or defibrillation may stop the arrhythmia and allow institution of pacing as a prophylaxis against recurrence.

Temporary pacing in the paired and coupled pacing modes (still experimental) may also be used to control a tachycardia. In paired pacing the rhythm is captured by a single overdriving stimulus and a second impulse is interjected shortly beyond the vulnerable period of this beat in its early nonrefractory period. At this point the second stimulus fails to produce a significant mechanical response but results in an electrical response which almost doubles the refractory period of the myocardium. Ectopic beats cannot intrude during this period and it is frequently possible to almost halve the spontaneous rate of the paced chamber, atrium or ventricle. In the coupled mode the intruded beat is interjected at the end of a spontaneous beat and results in a similar prolongation of refractory time and reduction in effective mechanical rate. These modes are safest when atrioventricular conduction is intact and they can be applied to the atrium. Here loss of the coupled or paired sequence will result at the worst in an atrial premature contraction or atrial fibrillation. In the ventricle, loss of synchrony may result in competitive ventricular pacing or possibly ventricular fibrillation. In one case where paired pacing with an effective rate of 106 per minute was still too rapid, triple pacing reduced the rate to a tolerable 70 beats per minute.

Most tachyarrhythmias resolve after hours or days of treatment. Where they are persistent or recurrent, permanent pacing by implantable demand pacemakers (Cordis, Medtronic, American Optical) may be utilized.

The treatment of tachyarrhythmias that occur or recur after pacemaker implantation offers a special and increasingly important problem. In fixed-rate asynchronous pacing they result in competition. Interjected conducted beats or premature ventricular contractions are more common. If they cannot be suppressed by digitalis, quinidine, propranolol or procainamide and are of concern then the pulse generator should be changed to the noncompetitive demand mode. In atrial synchronous pacing triggered tachycardias may result from atrial tachyarrhythmias. Here digitalis may slow the ventricular response by converting a slow coarse atrial fibrillation to a fine rapid rhythm which is less likely

to trigger the atrial sensor If this is ineffective and drugs cannot slow or convert the atrial tachyarrhythmia then the pulse generator should be changed to an atrially insensitive ventricular demand mode.

Temporary overdriving of implanted pulse generators is now possible with several systems. This is accomplished in General Electric asynchronous and Medtronic asynchronous and demand models by the use of specific special radiofrequency transmitters. In the Cordis atrial and ventricular synchronous generators, it is effected by 3 to 5 Ma impulses from any external pulse generator with one electrode placed over the pulse generator and the other on the contralateral side of the chest or abdomen

The problem of catheter electrode-induced arrhythmias during electrode insertion is not one of major magnitude. Repositioning will relieve virtually all mechanically induced single or multiple premature contractions Occasionally overriding pacing or antiarrhythmic medication may be needed to suppress irritability when repositioning fails. Very rarely a run of tachycardia or fibrillation may occur Whether this is spontaneous or induced repositioning and cardioversion or defibrillation may be required before positioning can be completed

The flexibility and utility of artificial cardiac pacing alone or in combination with antiarrhythmic drugs, is now generally recognized Facilities for its use should be available routinely in intensive care and recovery units or on cardiac emergency carts. Laboratory or bedside kits, containing all requisite equipment, are of great help in expediting its initiation and should be developed to meet the needs of each facility or institution Personnel trained in the use of these methods are increasingly available and contribute greatly to the improved control now possible in patients with tachyarrhythmias.

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Annotations

Backward masking*

In most physical diagnosis textbooks only casual mention is made of the psychoacoustical phenomenon of masking. Those texts devoted solely to the cardiovascular system usually discuss masking in relation to the difficulty hearing a relatively less intense sound which follows a more intense murmur.[1-3] One text discusses many examples of masking and defines it without specifying the sequence of the more and less intense sound. The sequence of the loud sound masking a subsequent less intense sound is, however, generally accepted as masking. Examples of the reverse sequence, however, have been described. Butterworth and associates' recorded heart sounds on tape and found that an inaudible, less intense sound followed by a loud murmur could be heard when the tape was played in reverse. Ravin also mentions that S_1 may be difficult to appreciate when followed by a loud pansystolic murmur. These may be examples of backward or retroactive masking.

We have observed an interesting physical finding which is another example of this phenomenon. If a loud opening snap is heard along the left sternal border, it is difficult to appreciate splitting of S_2 into its two components. An error may be made in assuming that the opening snap is loud pulmonary closure (PC) sound. Only when one is able to hear splitting in a different auscultatory area, i.e., first left interspace, where the opening snap is not quite as loud, can one appreciate distinct splitting of S_2.

This phenomenon may be demonstrated with a sound simulator.† An opening snap (OS) was simulated and its intensity, pitch, and the time interval between it and simulated aortic closure (AC) varied. The following has been found. (1) The closeness of OS to S_2 is important in detecting splitting. If the AC-OS interval is short, i.e., 50 msec., splitting is difficult to appreciate. If AC-OS is 75 msec. the difficulty is less, and is not present at 100 msec. AC-OS interval. (2) The louder the opening snap the more difficult it is to detect splitting of S_2 into aortic closure and pulmonic closure. (3) A high-pitched OS diminishes appreciation of splitting of S_2 more than a low-pitched OS. (4) A most important relation is, of course, the AC-PC interval. If this is relatively long, then the splitting is heard despite a loud, high-pitched OS. If the AC-PC interval is 25 msec., it is very difficult to detect splitting in the presence of a loud OS, especially if the AC-OS interval is relatively short, e.g., 50 msec. (5) Fast heart rates in general make detection of close splitting more difficult and the presence of a loud OS close-in seems to accentuate this somewhat. (6) Ordinarily a relatively loud AC and a less intense PC make it difficult to note splitting. This is usually attributed to masking. This would be an example of forward masking. If one adjusts the sound simulator so that AC is loud and PC relatively quiet but both audible, and then introduces a loud, high-pitched OS, splitting is no longer detectable. If PC intensity is increased, splitting may again become discernible. Thus, the relative loudness of the two components of S_2 influences backward masking by the OS.

Forward masking is often demonstrated to students by producing a loud AC which makes it difficult to detect PC, the latter becoming clearly audible as the volume of AC is reduced. When this procedure is reversed (i.e., adjust AC to have a low intensity and make PC loud), backward masking of the low intensity preceding sound cannot be demonstrated with physiologic sound intervals and the type of sounds produced by the simulator. If one produces a clearly audible S_1 with the sound simulator and follows this by a loud murmur, it is very difficult to appreciate the S_1 if the murmur is pansystolic, i.e., starts immediately after S_1. If a loud ejection murmur is produced which commences after a pause following S_1, then S_1 remains audible. This emphasizes that backward masking occurs only when the sounds are closely related in time.

Much psychoacoustical research on masking[1-4] has dealt extensively with simultaneous tones and is not clearly applicable to the nonsimultaneous auscultatory phenomena. Retroactive or backward masking is a less well-known phenomenon, recently extensively studied by Miller,[10] Elliot,[11] Pappas[12] and others, with nonsimultaneous tones. Miller[10] found a quite unexpected result that for masked frequencies higher than the masking frequency masking is greatest when the masked tone *precedes* the masking tone by $\pi/4$ radians (1 or 2 msec.). Licklider[13] explains retroactive masking as synaptic facilitation letting intense neural activity proceed up the auditory pathway at a faster pace than weak neural activity. Apparently the activity set off by the intense masking pulse catches up with that set off by the weak masked pulse by the time the latter activity reaches the auditory cortex.

Thus, in addition to masking in which a less intense sound is masked by a preceding more

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†[illegible] Phonocardio Simulator, Los Angeles, Calif.

sound, backward or retroactive masking occurs and may be of importance in auscultation. It makes splitting of S_2 difficult to hear when followed closely by a loud opening snap and probably explains the difficulty appreciating S followed closely by a loud systolic murmu

Summary

Forward masking occurs when a less intense sound follows a more tense one, nd is difficult to pprecuate Backward masking occurs when the less tense masked sound precedes the louder sound Examples of this situation are (1) the dif ficult in appreciating spl tting of S_2 followed closely by a loud opening snap (2) difficulty hearing S f llowed by a loud pansystolic murmur

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Hemodynamic alterations in acute myocardial infarction with shock

The hemodynamic tudies shock due to myocardial infarction ha not pointed out a typical pattern of alterations. Several patients ha e a reduction of the cardiac index (CI) and high total peripheral resistance (TPR) others have a low CI and TPR w thin normal limits others ha e a very low TPR and normal or high CI Because of these variations, there can be no one theory on the pathogenesis of shock following myocardial infarction. There are few detailed hemodynamic studies in man. The total umber of cases eported in the literature is scarcely above 100 Therefore we believe that any discussion of the physiopathology and pathogenesi of the myocardial inf rction shock should be based on the study of all the ailable data. Interesting information arises f om the comparison between the data obtained in patients with hock due to myocardial infarction nd in patients with uncomplicated myocardial infarction.

The values of CI and TPR (expressed as the in erse-to-conductivity ratio) of patients with shock hav in a Cartesian diagram different distribution as compared t the one of patients ithout shock (Fig 1) The division bet een the two groups (straight line calculated ith the least square method) seems to us surprisingly clear if con sider all the possible sources of error in such a comparison. The calculated line ca represent an esti mat of the critical threshold" below hich shock develops.

The average arterial pressure (AP'm), hich corresponds t the v lues of CI and TPR indicated f om the straight l ne of Fig 1 has hyperbolic form when plotted, which has demonstrated on the tridimensional diagram of Fig 2.

We ish to underline these points of interest. (1) The cases hose CI wa lower than about 1 3 L. per minut per square meter present shock for

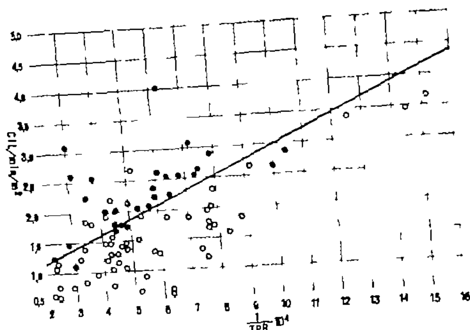


Fig. 1

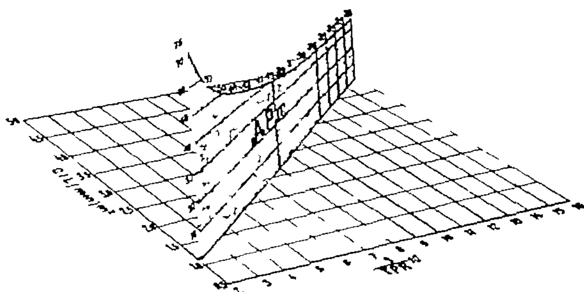


Fig. 2

any alue of TPR. Therefore, drugs which ary only the TPR probably d not impro hemodynamic conditions (the lnt points in Fig. 2 will be shifted along he abscissa). (2) I some of the cases, the behavior of the TPR in response to reduction in CI seems cord on the appea nce of shock. However large variation of the TPR could replace an even modest ef ect on of the CI. (3) I a few cases the TPR is ery low of the CI is not reduced or even high. (4 as the TPR in-

creases and the CI gets lower the "critical" APm rises. When the TPR is very low the APm goes to the asymtot In the critical line," for alues of bout 35 mm Hg. (5) The variable hemodynamic pattern in p tient with shock following myocardial inf rction underline the impossibility of nitary thesis for the pathogenesis of the shock based upon single measurement.

The sharp of patients with scardial in-

farction without shock, if confirmed by larger casuistry could be not only of theoretic interest but also have therapeutic implications. The critical value of the CI/TPR ratio could cause the reduction of the flow in some vital district of the body which many authors consider the essential pathogenetic factor for any kind of shock.

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Calcium metabolism and maintenance hemodialysis

Metabolic bone disease can prove a tragic complication of maintenance hemodialysis. An analysis of 639 survivors treated in European centers in 1967 revealed that gouty arthritis and secondary hyperparathyroidism were each found in 7 per cent of the patients and that there was evidence of metastatic calcification in 12 per cent. The average period of treatment in these patients was too brief to permit the emergence of the extremely devastating complications which have been reported from centers with longer experience.[2] Workers in Seattle[4] report clinical evidence of metabolic bone disease in 11 out of 26 patients dialyzed for more than two years. A progressive rise in the alkaline phosphatase which may take two years to reach abnormal levels is an ominous sign which may presage the development of demineralization, bone pain, and pathologic fractures.

Alimentary calcium balance in these patients is almost uniformly negative[4] but vitamin D metabolism is apparently normal. Therapy with vitamin D carries great potential dangers and has caused death due to myocardial and pulmonary calcinosis. Fear of inducing metastatic calcification has inhibited any deliberate attempt to compensate for negative alimentary balance by raising the calcium concentration of the dialysis fluid.[4-6]

With the risk of secondary hyperparathyroidism on the one hand and metastatic calcification on the other, it is of considerable importance to define the optimum calcium concentration of dialysis fluid for maintenance hemodialysis. Previous investigators of this problem[4,8,9] estimated calcium balance during hemodialysis indirectly from the arterio-venous difference across the dialyzer; they were concerned chiefly with acute observations and have not included any consideration of phosphate metabolism. The question has recently been approached with a combination of acute and long-term observations carried out at Fulham Hospital, London. Direct measurement showed that the external calcium balance during dialysis depended on the gradient between the plasma ultrafilterable calcium and the calcium concentration of the dialysis fluid. A gradient exceeding 1.0 mg. in either direction resulted in a net transfer of about 500 mg. of calcium during a 14 hour dialysis. Changes in plasma calcium did not correlate with measured external balance; the maintenance of a normal plasma calcium at the end of a dialysis in which negative balance occurred was thought to be a measure of the effectiveness of the response of the parathyroids. The removal of calcium by dialysis is a known stimulus to parathyroid activity.[10] It is concluded that the calcium concentration used should not be less than the plasma ultrafilterable calcium. In the patients studied, plasma proteins and arterial pH values were within the normal range before the start of the dialysis period, and the mean ultrafilterable calcium was 56.7 per cent of total plasma calcium.

In long-term studies it was found that raising the dialysis-fluid calcium concentration from 5.0 to 6.0 mg. per 100 ml. both caused regression of hyperparathyroidism and diminished the likelihood of metastatic calcification. When the concentration was raised to 6.5 mg. per 100 ml. gastrointestinal symptoms, presumably due to an increase in g... stric

acidity produced by the transient hypercalcemia,[14] occurred in some patients.

These patients were all dialyzed for at least 14 hours on two occasions each week, a total of 28 hours of dialysis. A patient is described in whom a progressive rise in alkaline phosphatase was arrested and the radiological changes improved following the increase in calcium concentration. Metastatic calcification appears to have been prevented by not permitting the calcium x phosphate product to rise above 75. Oral aluminum hydroxide was given when this product was exceeded, but it was rarely required because the plasma phosphates both before and after dialysis fell progressively following the introduction of the higher calcium concentration. In one patient with persistent hypercalcemia in excess of 11.0 mg. per 100 ml. for nearly one year due to parathyroid autonomy and in whom the calcium x phosphate product was controlled with aluminum hydroxide, there was no radiologic, ophthalmologic, or histologic evidence of the development of soft-tissue calcification.[15]

Progressive lowering of the plasma phosphate was thought to be due to efficient dialysis,[16] involution of hyperparathyroidism, and the deposition of calcium phosphate in unmineralized osteoid following the removal by dialysis of ultrafilterable inhibitors[17] of calcification. In some patients the fall in plasma phosphate has been extreme and frank hypophosphatemia (plasma phosphate less than 2.5 mg. per 100 ml.) has been recorded at the end of an interdialysis period.[18] This astonishing finding in anephric patients consuming diets with a normal phosphate content has been interpreted as indicating a high requirement for bone mineral, and calcium phosphate supplements have been given.

It is recommended that the calcium concentration of dialysis fluid is kept between 5.8 and 6.2 mg. per 100 ml. To achieve such a narrow range when seasonal variations in the calcium concentration of water supplies may occur,[19] it is probably necessary to use distilled, deionized, or softened water and to add calcium to the salt concentrate used. Adequate monitoring of the water processing is needed to avoid the risk of the "hard water syndrome"[20] and of killing patients with accidental hypercalcemia.

Other elements may also prove important in the pathogenesis of renal osteodystrophy in patients treated by dialysis. Hypomagnesemia is a stimulus to hyperparathyroidism.[21] The role of fluoride[22] and of other trace elements is largely unexplored. At Fulham a magnesium concentration of 1.2 mg. per 100 ml. and a fluoride concentration close to that of normal plasma (0.014 to 0.019 mg. per 100 ml.) have been used.

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A rapid bedside method for the control of heparin therapy

Heparin therapy has traditionally been controlled by the whole blood-clotting time. With the advent of widespread hemodialysis, the time and effort devoted to performing this test is of economic significance and the value of the results doubtful, as busy personnel may not observe the tubes frequently and the information provided by the long clotting time may no longer be relevant to the heparin concentration in the patient by the time the result is obtained. An accelerated test is clearly desirable, but the alternative methods described in the literature are difficult to use outside the laboratory. A simple rapid method suitable for use at the bedside or in the dialysis unit by personnel unaccustomed to coagulation tests and requiring no additional facilities has been developed. Results may be interpreted graphically in terms of the equivalent whole blood-clotting time.

The effect of heparin on number of clotting tests was examined, and the partial thromboplastin time was selected as potentially the most useful test. As usually performed this requires anticoagulation, centrifugation, incubation, recalcification, and a 37° C. water-bath.

The test as finally modified is performed by withdrawing 0.4 ml. of blood from the dialysis tubing or vein with a 2.5 ml. plastic syringe and adding it to a glass tube containing 0.1 ml. of Platelin (Warner-Chilcott, Morris Plains, N. J.) and 0.1 ml. of kaolin solution. The tube is shaken lightly or the tip flipped with the finger tip once to ensure adequate mixing and then tilted approximately every 15 seconds and the end point observed visually. A result equivalent to whole blood-clotting time of 30 minutes may be obtained in 200 seconds.

The reagents are standardized, freeze-dried platelet-factor reagent containing rabbit brain cephalin (Platelin) and a solution of kaolin (level) 20 mg. per 100 ml. in imidazole buffer. A variety of platelet factor reagents containing either kaolin or celite are commercially available and provide satisfactory results, but provide a somewhat slower test. Reagents may be added to test tubes in the morning for the day's tests. The tubes may be refrigerated but should be brought to room temperature prior to test.

In the control of heparin therapy the whole blood-clotting time is often done at room temperature and the error introduced (of the order of 30 per cent from 21 to 27° C.) is disregarded as being unimportant for clinical purposes. The test described is equally satisfactory. It is also suitable for use in a constant temperature water-bath and may be substituted for constant temperature clotting times.

It is a simple matter to introduce the test along with whatever modification of whole blood-clotting time is in use and to plot the results on ordinary graph paper. A useful regression line can be drawn after a few dozen tests and used to interpret further results in terms of the accustomed clotting time. In this way variations introduced by different source of reagents, glassware technique, and end-point determination will be taken into account.

Referring to the test as "An Whole Blood Activated Partial Thromboplastin Time" is unwieldy and the acronym HAREM Test (Heparin Assay Rapid Easy Method) seems justifiable, the chief virtues of the test being ease of performance and rapidity.

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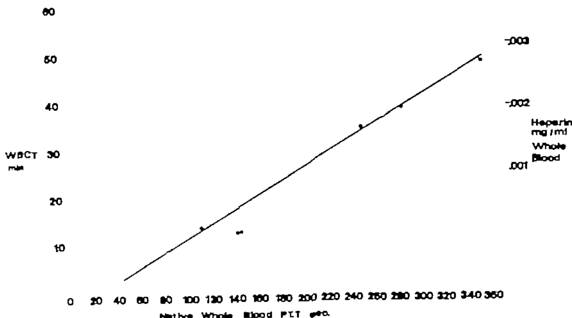


Fig 1

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Letters to the Editor

Relieving angina

To the Editor

I thought Dr. Zimmerman's editorial in the May issue of the AMERICAN HEART JOURNAL was quite penetrating and timely. There certainly is confusion in the mind of many cardiologists as to whether the so-called Vineberg procedure or any of its many modifications has any merit. Most people performing the operation state that it relieves angina.

Unfortunately, the relief of the symptoms has not always been well-correlated with anastomoses between the implanted artery and the coronary circulation. The relief of angina by any means is rather perplexing. All cardiologists are familiar with the effectiveness of placebos in the treatment of this condition as well as emotional support and many other factors. Angina frequently disappears spontaneously should the emotional stress that was producing it be removed. To some of us, therefore, performing a major surgical procedure to relieve angina pectoris is similar to calling a third alarm in order to control a kitchen fire.

Unfortunately, some of the pioneers in the field of surgical relief of angina have, to date, failed to give us the statistics on the long-term survival rate of such patients. It is necessary to find some rather objective methods to evaluate the benefits of this procedure. Such a test will be met by the performance of an experiment using the double blind technique. One group of patients with angina pectoris would receive the myocardial implant and another group would have the identical operation performed minus the implantation of the artery.

Such an experiment does present many difficulties. Surgeons are loath to subject patients to potentially dangerous sham operations. Nevertheless, with diligence and care such a procedure could be carried out.

Many of us recall how effectively Diamond, Kittle and Crockett demonstrated the inefficacy of bilateral internal mammary artery ligation, which was also widely praised as a treatment for angina pectoris. It seems to me that unless surgeons active in this area are willing to perform such an experiment, the attempts to evaluate surgery for the relief of coronary arteriosclerosis will remain unsatisfactory and confusing.

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Hypolipidemia in anemia

To the Editor

With reference to a recently published annotation (AM. HEART J. 76:849, 1968), we would like to report our findings on blood lipids in patients suffering from anemia.

Serum cholesterol, phospholipid, and triglyceride were estimated in 50 adult patients, 15 males and 35 females. Thirty-two of these patients were suffering from an iron-deficiency type of anemia. The values (mean ± S.E.) for various lipids fractions were: serum cholesterol, 101.4 ± 5.7 mg. per cent; phospholipid, 138.6 ± 7.3 mg. per cent; triglyceride, 66.0 ± 5.6 mg. per cent. No significant difference was found when lipid values were computed separately for the various types of anemia, i.e., iron deficiency, megaloblastic, and hemolytic. These values were significantly lower when compared with a group of age matched control subjects with normal hemoglobin levels. Improvement in the hematological status was associated with a rise in blood lipids.

The mechanism of hypolipidemia associated with anemia of diverse etiology is not known. This may be due to the effects of low oxygen-carrying power of the blood on lipid absorption, transport, and endogenous synthesis.

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Wedensky phenomena in the human heart

To the Editor

I read with interest the account of "Wedensky facilitation in the human heart" by Fisch and Knoebel in the July 1968, issue of the AMERICAN HEART JOURNAL. An alternate explanation for the effective ventricular response to subthreshold electrical stimulus near "p" wave would be that atrial contraction brought the catheter tip closer to the ventricular endocardium or that the addition

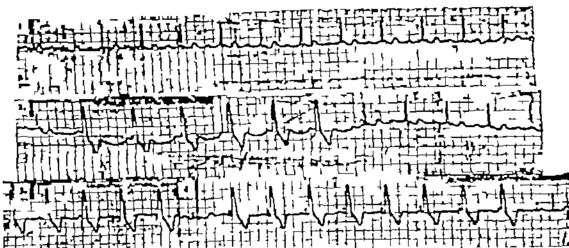


Fig 1

effect of the mechanical stimulus of the catheter under pressure from the trial contraction and the electrical stimulus as enough t overcome the threshold in the entricle. I the case reported by Fisch and Knoebel an epicardial pacemaker may have been i use but even so mechanical forces transmitted directl through the entricle or t an electrode loop overlying the atrium are concei able

Mechanical factors related t trial activity in the presence of intracardiac catheters and elec trodes should be expected to occasionally influence entricular electrical responses. The enclosed trac ings (Fig 1) provide possible example. All are of the same lead in the same patient and were taken within few moment of each other Tracing 1 was taken before catheter insertion and shows first degree A V block (0 32 sec.). Tracing 2 was taken shortly after the transvenous insertion of bipolar pacing catheter but prior to onset of pacing The catheter loop distended the right trium perhaps accounting for the slower rate Note the shortened P R interval (0.18 sec.) and widened QRS associ ted ith some beats I tracing 3 there are large pacing artifacts (note ink dot over every pacing artifact) followed by entricular complex iden tical to the widened QRS in tracing 2 and suggesting an identical origin, one from mechanical and one from electrical stim lation I tracing 4 low am plitude electrical stimulu seems to elicit en tricular response only in conjunction ith p wave t time hen A-V transmission is presumably blocked. This may represent electrical-mechanical summation effects.

Frequent difficulties may ery likely be expected in separating mechanical and electrical phenomena hen wires or ca beters ar in or on he heart.

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Reply

T the Editor

It is quit possible that the phenomenon observed by us may be explained on the basis of the mechanism suggested by Dr Goldberg A search for nd careful study of similar cases may ultimately resolv the question of existence of the various Wedensky phenomena in the human

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1 Editorial. Wedensky observations, Circulation 35:619 1967

Incidence and management of supraventricular arrhythmias after acute myocardial infarction

T the Editor

Jewitt, Balcon, Raftery and Oram, the authors of the abov paper published in your JOURNAL February 1969 compare the mortality rate of their patients, who developed atrial tachycardia and flutter following acute myocardial infarction, with that of other series, including ours in Australia. The implication is that their lower mortality rate of 23 per cent in 17 patients compared to ours of 61 per cent in 18 patients, supports their conclusion that DC shock is the treatment of choice in these arrhythmias.

Although I agree that rapid reversion of arrhythmias will often improve the immediate hemodynamic situation, I wish to re-emphasize the message of the paper namely that there are a number of factors influencing the short-term mortality rate following acute myocardial infarction. Therefore it is dangerous and invalid to draw conclusions from mortality figures related to the incidence or treatment of any specific arrhythmia. As shown in our paper the clinical severity of infarction as gauged on admission hypotension heart failure, cardiogenic shock, subsequent occurrence of other serious arrhythmias in the same patient, and finally the frequency and accuracy of observation and recording of arrhythmias all affect the observed prognosis.

Thus, of our 18 patients with atrial tachycardia or flutter 4 patients were admitted with cardiogenic shock and all died. As the mortality rate from cardiogenic shock is universally high (85 to 90 per cent), it would not differ with different methods of treatment. Of the remaining 14 there were 5 patients admitted with hypotension or heart failure or both who, in addition to these associated supraventricular arrhythmias, developed two or more of ventricular tachycardia, ventricular fibrillation, advanced atrioventricular block or left bundle branch block, and of these 4 died.

We observed that the mortality rate of all our patients with severe infarction associated with two or more arrhythmias below the A-V node was very high, regardless of the occurrence of an associated supraventricular arrhythmia. Of the remaining 9 patients with lone or multiple atrial tachycardia or flutter 3 died. Therefore the mortality rates of these three groups were 100, 80 and 33 per cent respectively. It would be of interest therefore if Jewitt and associates compared their results by classifying their 17 patients into the above groups. This may permit a more meaningful comparison.

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REFERENCE

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Reply

To the Editor:

Thank you for the opportunity to reply to Dr. Stock's letter.

In our series of patients with myocardial infarction, we considered that early DC reversion with low-energy discharges was beneficial in the management of persistent atrial tachycardia or flutter particularly when associated with a rapid ventricular rate. We did not intend to imply that the lower mortality rate we observed in patients with these arrhythmias compared with that reported from Australia by Dr. Stock supported our conclusions. This would clearly be unreasonable as Stock and associates' paper was not concerned with the specific treatment given to individual patients.

We agree that a number of factors influence the short-term mortality rate following myocardial infarction. In a previous publication we did, in fact, discuss the problem of assessing mortality figures in relation to the development of specific arrhythmias. General factors relevant to this problem include the selection of patients, the type of monitoring system used, the presence of multiple types of arrhythmia in the same patient, and perhaps most important, as Dr. Stock suggests, the severity of infarction judged, when possible, in terms of the patient's hemodynamic response before the arrhythmia develops.

In our patients we excluded all arrhythmias occurring terminally in patients with cardiogenic shock or ventricular failure. Five of our 17 patients with atrial tachycardia or flutter exhibited all the features of cardiogenic shock on admission. Because sustained atrial tachycardias may be associated with marked hemodynamic consequences after myocardial infarction all 5 were treated by early DC countershock. 3 survived to leave the hospital. It is our experience that when cardiogenic shock is associated with an ectopic tachycardia or advanced heart block, the mortality rate is not necessarily as high as that in patients with cardiogenic shock who remain in sinus rhythm. Ten of the remaining patients were either in heart failure or hypotensive on admission. 2 died, one from progressive myocardial failure and the other following a recurrence of atrial tachycardia with advanced atrioventricular block. In 2 further patients, the clinical assessment on admission indicated mild episodes of infarction and the atrial arrhythmias were transient. Both survived.

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REFERENCE

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Second heart sound in coronary artery disease

To the Editor:

I refer to the above paper published by Caulfield, Smith and Franklin in the February 1969 issue of the AMERICAN HEART JOURNAL. The authors in the introduction state that they are unaware of the documentation by phonocardiography and of the frequency of paradoxical splitting of the second heart sound in coronary artery disease. Although due to the nature of the illness no patient of theirs was studied during the acute phase of infarction, they concluded that "the incidence of

paradoxical splitting may well be higher in patients during an acute ischemic episode or in those suffering from more severe form of disease, who need further evaluation. They found normal splitting in 20 patients who had previously suffered a myocardial infarction.

I refer the authors to my findings in a clinical and phonocardiographic study of 37 patients with acute myocardial infarction. Only 4 patients had phonocardiographic evidence of paradoxical splitting of the second heart sound. The low incidence differs from the clinical observations of Yurchak, Cohen, and Dickerson and are in keeping with those of Caulfield and associates.

It is of interest that in almost all patients with acute myocardial infarction, there was some abnormality of the heart sound or murmur the commonest being an abnormal splitting of the first heart sound.

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REFERENCE

1 Stock, E. Auscultation and phonocardiography in acute myocardial infarction, M. J Australia 1 1060 1966.

Reply

To the Editor:

Our study was a systematic auscultatory and phonocardiographic analysis of the second heart sound in patients with coronary artery disease. Phonocardiography revealed normal splitting of the second sound in all 20 patients studied and illustrated the need for reference (indirect carotid pulse) in the assessment of the second sound. Although Dr Stock and others have written about the second sound in coronary artery disease, ours remains to my knowledge the first to include phonocardiography in the assessment of all patients studied, which we believe is necessary for accurate appraisal of splitting of the second sound.

We were unaware of Dr Stock paper and thank him for calling attention to it. The fact that he was unable to perfectly correlate auscultatory and phonocardiographic findings of splitting of the second sound further enhances our contention that phonocardiography with a carotid tracing is needed to correctly assess the second sound. We agree with his findings that a paradoxically split second sound is uncommon in coronary artery disease.

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NOTICE. Beginning in January 1970 abbreviations for journal titles in references are to follow the style used in the Cumulated Index Medicus. These abbreviations may be found in the Subject Index of the Cumulated Index Medicus, as well as the publication entitled *List of Journals Indexed in Index Medicus*, published by the National Library of Medicine and available at nominal price from the Superintendent of Documents, U S. Government Printing Office, Washington, D C 20402.

Book reviews

CARDIAC DIAGNOSIS. By Peter Carson, M.A., B.M. (Oxford), M.R.C.P. (Lond.), F.A.C.C. New York, 1969. The Blakiston Division, McGraw-Hill Book Company. 576 pages. Price $17.50.

Dr. Carson has condensed some of the most important aspects of clinical cardiology into approximately 500 pages. The book is written for the practicing physician but should prove valuable to medical students, interns, and residents. The text is well written. The book is organized in the usual fashion for such monographs. The presentations are accurate though incomplete. A fairly lengthy bibliography is included. The reader must realize that this relatively brief book must be supplemented by the medical literature and other textbooks of cardiology. The reader will be impressed with the clinical orientation of the book and the brevity of the presentations of the author's own ideas and experience. This a very good book for beginners and busy physicians.

PATHOGENESIS OF CORONARY ARTERY DISEASE. By Meyer Friedman, M.D. New York, 1969. The Blakiston Division, McGraw-Hill Book Company. 269 pages. Price $19.50.

Dr. Friedman has been interested in the pathogenesis of coronary artery disease and arteriosclerosis for many years. He has made many important contributions and introduced interesting theories. Nevertheless he like all others does not really know precisely the pathogenesis of coronary artery disease or arteriosclerosis. Certain factors are known to be related statistically but their pathogenicity remains unsettled. This is a very good book on coronary artery disease. It is well written and the color plates are elegant. The monograph is divided into two parts, experimental and clinical. The known factors are clearly presented but the author has not convinced this reviewer that we are any closer to the understanding of the mechanism by which coronary arteriosclerosis is produced today then we were over 50 years ago. Regardless this is a very good book which contains a good description of the author's own research and ideas as well as the aspects of the pathology concerned with coronary artery arteriosclerosis.

EPIDEMIOLOGY OF CEREBROVASCULAR DISEASE. By John F. Kurtzke, Berlin and New York, 1969. Springer Verlag. 197 pages. Price $14.50.

This monograph by Kurtzke condenses in a relatively small volume the important epidemiologic data on cerebrovascular disease. The convenience offered others interested in the subject by this monograph is considerable. The book consists of 13 chapters including such aspects of epidemiology as definitions and methods, validity of mortality data (from this reviewer's opinion they are most unreliable when obtained from the Bureau of Vital Statistics of the individual states and United States Government), general features, geographic distribution, race, and course. International data are also presented. The reliability of these data is also unknown. Kurtzke's book contains over 400 references and an appendix of many tables of usual epidemiologic information. This book is recommended to those interested in this aspect of cerebrovascular diseases.

CARDIAC CATHETERIZATION AND ANGIOCARDIOGRAPHY. An Introductory Manual. By David Verel, M.A., M.D., F.R.C.P., and Ronald G. Grainger, M.D., M.R.C.P., D.M.R.D., F.F.R. Baltimore, 1969. The William & Wilkins Company. 172 pages. Price $14.00.

This manual contains information related to techniques and interpretation of cardiac catheterization and angiocardiography. Sir John McMichael wrote an interesting history as a forward to this book on cardiac catheterization which relate his own brief experiences and difficulties with cardiac catheterization. The book is adequate for beginners but should interest others very little since it is only an introduction to the subject. The presentation is accurate, brief and lucid. The atlas of angiocardiograms and roentgenograms of catheterization with the catheters in place is valuable. The legend associated with each of the 116 figures in the atlas are extremely useful. This is a good manual to add to the others already available.

HYPERTENSIVE CARDIOVASCULAR DISEASE, Vol. I, no. 1. Edited by Albert N. Brest, M.D. Philadelphia, 1969. F. A. Davis Company. 332 pages. Price $8.00.

This book, edited by Dr. Brest, represents the first of three planned. The titles of the other two will be *Coronary Heart Disease* and *Cardiovascular Therapy*. The contributors are numerous and include physicians who have been concerned with hypertension for many years. The subject discussed include natural history, pathology, labile hypertension, hemodynamic phenomena, diastolic and renovascular hypertension, therapy and toxemia of pregnancy among many other

important clinical problems. Hypertension is an important and common disease of man. The introduction of antihypertensive drugs and other measures have made it possible for the physician to offer his patient effective therapy. This book, therefore, can be extremely useful to those who wish to learn about the management of hypertension. Students, interns, residents, and practicing physicians will find this to be a useful book, in fact, one to own. Unfortunately, there is not enough emphasis on diet and the psychologic aspects of the disease. Home recording of blood pressure and the relationship of hypertension to arteriosclerosis, another important cardiovascular disease, have received little emphasis in this book. The early and adequate control of hypertension is most important in the control of arteriosclerosis. This book contains a great deal of important and practical information.

MICROSCOPIC INNERVATION OF THE HEART AND BLOOD VESSELS IN VERTEBRATES INCLUDING MAN. By Professor A. Abraham. Oxford, 1969, Pergamon Press, 433 pages. Price $21.00.

This is a very good discussion of the innervation of the heart and blood vessels by one who has devoted his life to the study of these problems. The importance of the nerve supply to the myocardium and conduction systems and the blood vessels is well recognized. To have a clear and well presented discussion of the anatomic relationship of innervation of the heart to possible function is extremely important in research and therapeutics. Doctor Abraham has performed an important service to all of us in this excellent book. The illustrations are extremely good, the associated text is clear, and the bibliography is extensive. This monograph is highly recommended not only to investigators, but to students and clinicians as well.

Obituary

Robert Hebard Bayley

1906-1969

Dr Robert H Bayley noted cardiologist and Professor of Medicine at the University of Oklahoma Medical Center died April 11 1969 at the age of 62 following vascular surgery

Dr Bayley was born in Paterson N J and received the degrees of Bachelor of Science and Doctor of Medicine from Emory University Following his internship and residency training at the University Hospital Ann Arbor Mich he became interested in the application of mathematical principles to electrocardiography and became a lifelong friend and collaborator of Frank N Wilson whom he greatly admired

His first paper in electrocardiography Frequency and Significance of Right Bundle-Branch Block, was published in 1934 It had been preceded in the literature by papers on Right Aortic Arch (1932) Dynamic Dilatation of the Thoracic Aorta (1933) and Thyroid Crisis (1934) After four years at Ann Arbor he was appointed as a Resident Physician at the Leahy Home Tuberculosis Sanatorium Honolulu During this year he began his self training in mathematics. In 1936 he accepted an Instructorship in Medicine at the Louisiana State University In 1939 the first papers relating to the mathematical exposition of the electrocardiogram appeared They were Fundamental Relations of the Instantaneous Electrical Axis of Cardiac Accession and Potential Produced by Cardiac Muscle a General and a Particular Solution In 1944 he left an Associate Professorship in New Orleans,



Dr Robert H Bayley 1906-1969

to join the faculty of the University of Oklahoma as Professor of Medicine and Director of the Heart Station At the time of his death he was serving as the George L. Cross Research Professor of Medicine and Director of the Biophysics Section of the Department of Medicine

During his academic years Dr Bayley published many notable contributions to electrophysiology and electrocardiography On Certain Applications of Modern Electrocardiographic Theory to the Interpretation of Electrocardiograms which Indicate Myocardial Disease published in the AMERICAN HEART JOURNAL in 1943 has become a classic. Several observations on

injury and ischemic effects of coronary occlusion were published in the years 1944 to 1946. After the paper "Peri-infarction Block" was published in 1950 he devoted most of the following years to analyses of exploratory lead systems, th[e] "zero potential" and the electric field produced by arbitrary dipoles in models of circular and elliptical shape. Problems of nonhomogeneity attracted his attention later and became the bases of his most recent publications. Since 1950 he had published 16 papers reflecting his interest in these biophysical problems.

Dr Bayley was a member of many scientific societies and a recipient of numerous national and international awards. He was a member of the original research committee of the American Heart Association and was instrumental in establishing many of its present policies. He was one of the first Established Investigators of the American Heart Association and in 1959 he received a citation for distinguished service to research from this organization. He was a founding member of the Southern Society for Clinical Investigation. He was an Honorary Fellow of the American College of Cardiology

"Bill" Bayley's many friends and associates will miss greatly the presence of his quiet enthusiasm modesty and genius. His clinical acumen was superb and tales of his diagnoses from the electrocardiogram and at the bedside are legendary. He had an abiding personal interest in his friends students, and associates. He was a gifted teacher with an uncanny ability for analysis and synthesis which served as a constant stimulus to his students. His research efforts were marked by precision complete honesty and originality. His devotion to his research endeavors was at times all-consuming sometimes to the discomfiture of his less well informed colleagues. He frequently used his friends as a sounding board for ideas which in their mathematical complexity were clear only to their originator

Ironically he suffered from the same diseases for which he helped bring about better understanding. In recent years he was slowed down considerably by two episodes of myocardial infarction and severe intermittent claudication. Typically few people knew of his affliction.

An avid golfer in his younger years he later became an accomplished sculptor. He found relaxation in classical music

Throughout his career he was helped by the constant devotion of his wife Martha ("Martie") who survives him. There are two children Norman and Phyllis. Sharing their grief is a wide circle of friends and colleagues.

L. L. Conrad M.D.
J. M. Kalbfleisch M.D.
Oklahoma City Okla

SELECTED TOPICS IN CARDIOLOGY. The University of Texas Graduate School of Biomedical Sciences at Houston, Division of Continuing Education, will present a course on "Selected Topics in Cardiology" on Dec 1-4, 1969, in Houston, Texas. The guest lecturer will be Dr William Likoff, Professor of Medicine and Director of Cardiovascular Institute, Hahnemann Medical College and Hospital, Philadelphia, P. The primary discussions will be concerned with modern appraisal of patients with coronary heart disease, angina pectoris, cardiogenic shock, coronary care units, beta-adrenergic blockage in arrhythmias and angina pectoris, and surgical treatment of coronary artery disease.

For further information write: The University of Texas Graduate School of Biomedical Sciences at Houston, Division of Continuing Education, P. O. Box 20367, Houston, Texas 77025.

THE AMERICAN ACADEMY OF ALLERGY will hold its twenty-sixth annual meeting at the Jung Hotel, New Orleans, La., on Feb 14 to 18, 1970. Additional information is available from the Executive Office, 756 North Milwaukee St., Milwaukee, Wis. 53202.

THE DIVISION OF CLINICAL PHARMACOLOGY, Departments of Internal Medicine and Pharmacology, University of Iowa College of Medicine, offers 2 to 3 year fellowship in clinical pharmacology to physicians with a minimum of 1 year of house staff training in medicine. Accepted candidates enroll in the Graduate College, take courses in biostatistics, experimental design, and advanced pharmacology and participate actively in research. Stipends are provided by training grant from the National Heart Institute. Applications may now be filed for the year beginning July 1, 1970 and for the year beginning July 1, 1971. Write to Dr William R. Wilson, Head, Division of Clinical Pharmacology, University of Iowa Hospitals, Iowa City, Iowa 52240.

NEW FELLOWSHIPS IN CARDIAC REHABILITATION. The Department of Rehabilitation Medicine of Montefiore Hospital and Medical Center has started a new program in cardiac rehabilitation which is recognized as the equivalent of one year of medical training by the American Board of Internal Medicine. It is unique in that it provides training in an area overlapping rehabilitation medicine and cardiology.

The clinical program permits participation in the activities of the rehabilitation medicine inpatient service and in the functional evaluation of patients with recent cardiac episodes. Training is also provided in the laboratory in the techniques of exercise electrocardiography, measurement of energy cost, various types of performance and exercise testing, disability evaluation, and work physiology. Field experience is gained in on-the-job monitoring and in medical supervision of exercise programs in the community for cardiac patients.

The program is under the direction of Jerome S. Tobis, M.D., Chief of the Department of Rehabilitation Medicine, and Lenore R. Zohman, M.D., Director of the Work Physiology Unit, a modified cardiopulmonary laboratory within the department.

Fellowships are available to residents with one year of training either in internal medicine or physical medicine and rehabilitation. Stipends range from $10,250 to $12,250 depending on qualifications. Positions are available starting January or July 1970.

For more information contact: Mr Nathan Zamoff, Education Coordinator, Department of Rehabilitation Medicine, Montefiore Hospital and Medical Center, 111 East 210th St., Bronx, N.Y. 10467.

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